STUDIES IN ENCEPHALITIS

J. H. STEPHENS

C O N T E N T S

PREFACE

The influenza pandemic of 1957 reached its peak in Renfrewshire in the early autumn of that year and about the same time it became generally known that some patients who had shown symptoms of respiratory disease were also affected by disorders of the central nervous system. In most cases the illness was mild and the patients recovered completely within a few days. A few patients, however, with more severe symptoms were admitted to hospitals in Greenock. In the period August - January 1957-58 seven such patients were admitted and four of these died. Since fatal cases in any epidemic are in a minority, confirmatory evidence was sought for the existence of similar cases elsewhere.

In the first instance, enquiries were pursued on grounds of clinical and pathological correspondence and two cases (cases 11 and 12) contemporary with one of the Greenock cases (case 4) and presenting remarkable clinical similarities, were traced in Glasgow. As a result of further studies on the original material at Greenock it became evident that herpes simplex virus might have an aetiological role in the outbreak. The scope of enquiry was therefore enlarged and all virological and serological records held at Glasgow were surveyed to find cases with evidence for implication of herpes simplex. Six such cases were identified (cases 13 - 18) and are included in these studies. The clinical material presented is completed by a further small group of three cases (cases 8, 9 and 10) of encephalitis occurring in the spring and early summer of /

of 1959 at Greenock. Since then no comparable cases of encephalitis have been encountered at Greenock to date.

Patients comprising the Greenock group of 1957-58 (cases 1 - 7) were all available for clinical examination by the author as were those in the second smaller group of cases in Greenock in 1958-59 (cases 8 - 10). Detailed survey and daily assessment of progress were therefore possible while these patients remained in hospital and in several instances the patients could be studied in clinical follow-up after discharge. It was noted, however, that where recovery was apparently complete, the cooperation of patients in follow-up was sometimes lacking and the movement of individuals out of the area frequently cancelled long-term plans of this nature. Necropsy was undertaken by the author in cases 1, 5, 7 and 8 and the brain in case 15 was made available for personal investigation. Virology could be undertaken only in Glasgow and there was unavoidably some delay in presenting the material. While this was kept to a minimum it may have affected the results obtained. Virological investigations in Glasgow, which were the responsibility of the virological staff there, were followed as closely as the exigencies of peripheral service permitted.

Cases 11 and 12 were traced on clinical grounds as a result of the cooperation of the psychiatric staff in Glasgow and cases 13 - 18 after examination of virological and serological records held in Glasgow. Because of the delay inherent /

inherent in procedures of this kind clinical examination was often precluded. In some instances also, patients were treated in areas remote from Glasgow and clinical records were the only source of information. The clinical and laboratory staffs concerned in this work gave, in all cases, the highest degree of cooperation and help and this is gladly acknowledged, but it will be appreciated that in no instance was the investigator free to command procedure which remained the responsibility of the clinical and laboratory staffs concerned.

These studies in encephalitis have been pursued in conditions which afford peculiar difficulties to the investigator in addition to those furnished by unknown aetiology and pathogenesis. The difficulties arise from numerous sources, in part, administrative, and, in part, deriving from the clinical requirements of the patients. Patients with signs of encephalitis are admitted to general medical hospitals or hospitals for infectious diseases and some are transferred between these reception centres. Clinical diagnosis is difficult and generally is by exclusion. The patients, on admission, are frequently very ill and it is often necessary to exclude the presence of a space-occupying lesion within the skull; for this purpose, transfer to a neurosurgical centre is necessary. When these studies are complete the patient is returned to the original hospital or to another in the region of his home. If the disease /

disease becomes chronic and the patient seems likely to survive for some time it becomes necessary in some cases again to transfer him to a suitable institution. The disease, not infrequently, is terminated by death and the necessity, from the point of view of the investigator, for rapid necropsy and the preservation of suitable material for virological and morbid histological studies is often not appreciated by those who may be in charge of the patient at the time. This appears all too clearly in the extensive literature on this subject and has been borne out by experience in the present investigations. Even when careful arrangements have been set in train in particular cases failure in communication has resulted in irretrievable loss of material. In other instances, where cases have emerged retrospectively after examination of clinical or serological records, it has been usual to discover that investigations made during the acute period of illness are incomplete. Where the illness has been very mild and has resulted in rapid recovery the stimulus to pursue clinical investigations has been lacking and they have not been carried out. In other instances death has supervened so rapidly, that serial studies, especially in serology, have not been possible. All these problems, in generous measure, have been encountered in the present series. Nor does it seem possible in the absence of special administrative changes that these conditions can be substantially improved.

The /

The conditions under which these observations have been made therefore preclude the detailed application of appropriate scientific criteria in any particular case. Nevertheless, the findings as a whole are not without interest and are presented as a contribution to studies in this disease complex.

CHAPTER I

INTRODUCTION

EPIDEMIC INFLUENZA AND ENCEPHALITIS

Epidemici paucissimi novi sunt.

Scheffelius

Rubric: 1727.

The association of epidemic influenza and outbreaks of encephalitis has engaged the attention of many authors from classical times to the present day although many early reports are difficult to evaluate because of the absence of established criteria of diagnosis and reference. The syndromes described are often applicable to a variety of respiratory and nervous disorders of comparable symptomatology and precise identification of the diseases described is not possible at this remove of time. Nevertheless, many authors have left careful descriptions of clinical syndromes from which it is possible to infer diagnosis with some degree of assurance. If such reports were few, or if the association of these diseases were but rarely recorded, the value of the evidence would be slight. As it is, medical literature from the fifteenth century onwards abounds in references of this kind and these collectively provide an impressive body of evidence.

From the literature it is apparent that authors of the fifteenth century were conversant with earlier observations on this subject and allusions occur repeatedly which suggest that a general awareness of the epidemiological implications of the problem has been part of the medical philosophy of western Europe at least since this time. In many cases eponymous references imply international acquaintance with certain syndromes and the transference of nomenclature from one country to another in Europe goes some way to suggest a common /

common ground of agreement in medical matters. At various times attempts were made to assemble the evidence of earlier authors and to subject it to critical scrutiny. This tendency to review earlier work and to seek evidence therein of an epidemiological relationship between influenza and encephalitis was most marked at times when current epidemics of influenza were associated with numerous instances of nervous disorder. Such penal visitations in later years gave rise to extensive studies which form valuable landmarks in the literature. In the mid-nineteenth century after the influenza pandemics of the fourth decade many authors gave their attention to this problem and, of these, Ozanam (1835) essayed the task of compiling a history of epidemic encephalitis and Thompson (1852) collected and published many observations of earlier writers. Similarly, the influenza pandemic of 1918 and its attendant outbreak of encephalitis lethargica promoted interest in earlier records. Crookshank (1919) is particularly associated with this study and some account of the history of these diseases finds a place in the Ministry of Health Report of 1922. Thirty years earlier, individual authors had examined isolated cases of influenzal encephalitis and had reported their morbid histological findings yet this Report is probably the first in which scientific criteria are clearly established and it is the more valuable because it includes the opinions not only of British observers but also embodies a digest of the best Continental opinion of the day.

Although /

Although many references in the older literature are obscure and of doubtful interpretation, some are striking and suggest that the association of these diseases has been known from antiquity. Hippocrates, in discussion of an "ardent "fever and phrenitis which occurred early in Spring after the "cold had set in" mentions that his patients were "constantly "affected with coma in which they got no sleep, or with "insomnolency attended with pains". In the same context he writes ".....during this state of weather in the winter "paraplegias began and attacked many, some of whom died in a "short time for the disease was very epidemical."

In the period from the mid fifteenth century to the turn of the seventeenth century records are preserved in which wide epidemic prevalences were recorded without resolution into component diseases and in which symptoms which may have been due to various forms of meningitis, encephalitis and myelitis were described in relation to what now might merit the description of "disease-groups". An occasional reference however brings the relationship sharply into focus. In the influenza epidemic in France of 1481-2 Jean de Troyes writes of this epidemic "qui attaquoit aussi bien les grands et les "petits.....qui mettoit le feu à la teste.....maladie de "fievre et rage de teste". The influenza epidemic of 1529 in Germany included many cases showing affections of the cerebral nerves, pain in the head and stupor. The victims died within a few hours of the onset of the illness. Not all authorities were /

were agreed that the nervous symptoms observed were due to influenza and in Germany in 1529 a substantial body of opinion ascribed these severe forms of 'sudor Anglicus', as the febrile respiratory epidemic was widely known, to the eating of fish. Others held that rye was the source of poison and there is some evidence to suggest that botulism may have been prevalent at this time. Throughout this history there is a persistent ascription of various prevalences of nervous disorders to varieties of food poisoning and as late as 1820, outbreaks in Germany of what seems to have been poliomyelitis were attributed to the consumption of Swabian sausages. The epidemic of 1545-6 in Piedmont and Savoy included many cases with encephalitic symptomatology and similar cases were also observed in the pandemic of 1580. The epidemic of 1581 at Luneberg was attended by many cases of palsy of the head and limbs and Zeviani writing in 1804 of the influenza epidemic of 1597 in Italy brought forward evidence in favour of the view that the illness was an intensely nervous form of influenza and that stupor and catatonia were prominent symptoms in that outbreak. The influenza epidemic of 1657-8 in England was marked by a strange fever which gave rise to severe cerebral and nervous disorders and later in the same year the same illness in Copenhagen was attended by an epidemic of lethargy.

In the eighteenth century, systems of nosology were based on symptoms and the syndromes of generalised nervous diseases were referred to nervous, comatose, lethargic, stuporose /

stuporose, convulsive, apopleptic and paralytic fevers. These were generally considered as different elements of special epidemic constitution. Many patients in the Turin epidemic of influenza in 1725 showed comatose, cataleptic and convulsive syndromes and similar cases were recorded in the epidemic in Sweden in 1757. In London in 1775, many influenza patients died after the onset of the "comatose fever" of Sydenham.

In Russia the influenza epidemic of 1800-3 was noted as being extraordinarily 'cerebral' in its manifestations and the European epidemics of 1831, 1833 and 1836-7 gave rise to extensive literature on the incidence of encephalitis and myelitis. Lombard observed the influenza epidemics in Geneva in 1831 and 1837, and, in the latter year, made this significant observation "La grippe est souvent précédée par "une constitution éminemment nerveuse, dont les caractères "principes sont de porter le trouble dans les fonctions du "cerveau et des nerfs encéphaliques". The parallel in the Vienna epidemic of 1917 is striking. Cases of encephalitis following influenza were reported by Fürbringer (1892), Leichenstern (1892) and Königsdorf (1892) and the latter published a description of perivascular cuffing and lymphocytic infiltration of the brain. Strümpell in 1891 described a case of primary acute haemorrhagic encephalitis and many cases since this date have been reported by others.

In the early years of the present century opinions were divided in European schools on the aetiological importance of /

of influenza in cases of encephalitis. In Germany, where many authorities were of the opinion that there was a definite and important link between these diseases, there was general support for a causal relationship. The 1919 pandemic of influenza was preceded in Vienna by the appearance of the first cases of von Economo's disease (1917). In France, England, Wales and the United States of America, outbreaks of influenza and encephalitis lethargica were coincident during the years 1918-1921. In Spain encephalitis appeared at the end of the 1919-1920 pandemic and in Canada an outbreak of encephalitis lethargica in Winnipeg followed the epidemic of influenza after the interval of a year. Many important contributions to the Ministry of Health symposium of 1922 gave further details of the relationship between the diseases in England and Wales. An analysis of the concomitant or prodromal illnesses in a total number of one hundred and forty nine cases of encephalitis lethargica showed that one hundred and fourteen of these patients also had influenza. Of these, forty-one cases of influenza preceded the onset of encephalitis in 1919, and fifty-six in 1920. In spite of these findings the considered opinion of the Ministry was that there was no causal link between the diseases since they showed only a temporal relationship. Contemporary critics were not slow to argue that since spatial relationship was not in dispute and a temporal relationship was admitted it was difficult to see what further conditions were required by the Ministry before a causal link might /

might be recognised. American authors reporting the epidemic after it had appeared in the United States also were reluctant to accept the inference that the diseases were related. Thus, Neal (1919) pointed out that the evidence was entirely circumstantial, although the impression was widespread that encephalitis had not appeared in anything like epidemic form except in association with influenza and the same author drew attention to the previous epidemic in America of 1889-90 when the diseases had occurred together. In a large proportion of American cases of encephalitis lethargica in 1919 the onset of the disease was preceded by an attack of clinical influenza. Of the six cases reported by this author, four had clinical influenza about two to three weeks before nervous symptoms appeared. Neal felt compelled to admit that some relationship of unknown nature appeared to exist but she added a minatory rider on the value of unsupported speculation. About the same time, French opinion was canvassed on this topic and medical views were collected from many Departments of France and the concensus of opinion supported the possibility of a close relationship between the diseases.

Until the second half of the nineteenth century diagnosis was based largely upon clinical findings and medical opinion found little difficulty in postulating an aetiological relationship between epidemic influenza and associated nervous disorders since these conditions had appeared frequently close together in time. With the emergence of pathology as a subject in /

in its own right and with advances in morbid histological technique a new and powerful instrument was at the disposal of the diagnostician. Much of the early work in the new field of pathology was undertaken in Germany in the closing decades of the nineteenth century and the opinions of workers in the German schools came to be widely respected in Europe. From a modern point of view it is not difficult to criticize some of the conclusions reached by these early investigators who were unaware of many pathological mechanisms which are well known today. It is evident, for example, that in encephalitis these workers were unfamiliar with the wide variations in morbid histological findings which occur in various forms of this disorder and the first conclusions were promulgated after examination of only small numbers of cases. Much of this early work is distinguished by painstaking and detailed examination but the conclusions reached, from a modern viewpoint, were incomplete, although at the time of publication they seemed definitive. There is evidence to suggest that medical opinion throughout Europe in the first decades of this century was much influenced by the views of these pathologists and, as an ever larger number of cases of encephalitis was submitted to morbid histological diagnosis, the differences which emerged became increasingly difficult to reconcile with definitions previously laid down. It seemsprobable that the obvious discrepancies between the morbid histological findings promulgated as those of influenzal encephalitis by German workers /

workers and those constantly reported from many sources in cases of encephalitis lethargica, may have influenced a substantial body of medical opinion to deny that an aetiological relationship existed between the influenza pandemic of 1918-1919 and the epidemic of encephalitis lethargica which accompanied it. In this way the nervous disorder came to be regarded as a new entity with the eponym of von Economo's disease. It should be borne in mind, however, that the 1918-19 epidemic of influenza and encephalitis occurred at that point in the development of medical science when, for the first time, laboratory technique was sufficiently developed and facilities for examination sufficiently available in many countries, to enable morbid histological studies to be carried out in numerous cases. In this sense, the pathological entity described was a new disease to the pathologists who earlier had neither the technique nor the opportunity to familiarise themselves with it. Nevertheless there is a large volume of evidence to suggest that a disease clinically in close resemblance to encephalitis lethargica had occurred previously in many countries in epidemic form in association with epidemics of influenza.

The epidemic of encephalitis lethargica in 1918-20 was the first in which morbid histological studies were made on a relatively large number of cases and reports from many centres in various countries were compared. A broad measure of common agreement was acknowledged and the relevant section in the 1922 Report includes the findings of von Wiesner (Vienna), Netter /

Netter (France) and MacIntosh (U.K.). In addition, various other authorities reported independently and their findings again compare with those of the Report (Bassoe and Hassin 1919 (U.S.A.) Fano 1921 (U.K.). The general description thus furnished of the morbid histology in encephalitis lethargica in the third decade of this century does not agree with that of observers of the late nineteenth century in cases described as influenzal encephalitis. These early reports, chiefly concerned with macroscopic appearances, stressed the haemorrhagic character of influenzal encephalitis although Konigsdorf had described perivascular cuffing and lymphocytic infiltration in 1892. After Strumpell's early report in 1891 of primary acute haemorrhagic encephalitis many cases were subsequently described under various headings. The number of these cases attributed to influenza depended rather on individual preference than on objective evidence. On the whole the English and French observers were less inclined to accept this aetiology than were the German. None the less, haemorrhagic encephalitis in succeeding years came to be accepted by an important body of academic opinion as typical of influenzal encephalitis. This view appears to have originated in the German schools and was promoted by them at a period when German pathologists and morbid histologists were most influential in academic matters. The preoccupation of the time with exact morbid histological detail, not entirely unmixed with a certain dogmatism, lent authority to these concepts. It is not surprising, then, to read in the conclusions /

conclusions of the 1922 Report that ".....encephalitis "lethargica is not an influenzal encephalitis of which the "anatomical features are invariably those of acute haemorrhagic "encephalitis". The tendency to separate haemorrhagic encephalitis as an entity related to influenza was underlined by Juhl (1921) who reported the pathology of fatal cases of influenza at Kiel during the 1918-19 epidemic. In two hundred and eighty-five cases he observed twenty-six of haemorrhagic encephalitis. The lesions were distributed widely in the brain but were more numerous in the white than in the grey matter and included haemorrhages and congestion. The pathogenesis of haemorrhagic encephalitis is still unknown but there is some evidence to suggest that these lesions are most numerous in fulminating cases of rapid onset and short duration. Haemorrhages in encephalitis, as is well known, are often of ball or ring form and these lesions occur also in a variety of other conditions. With regard to the vexed question of the pathogenesis of these lesions, Fischer Wasels (1933) pointed out that the destruction of cerebral tissue can occur in one, or in several places, as a direct result of trauma or of poison, or, indirectly as a result of circulatory disturbance. This author was of the opinion that certain products of cell lysis are formed as a result of tissue destruction and these substances act on vessel walls and give rise to angionecrosis. Wolff (1937) was substantially in agreement with this view and came to regard these lesions not as haemorrhages in the ordinary sense of the word but as reactive /

reactive formations ('reactiv Bildungen') which block the damaged portion of a vessel. Discussing the appearance of these lesions in head injury he showed that ball haemorrhages were the first to appear but were not seen in cases where the patient had survived less than two hours after injury, while ring haemorrhages appeared only in patients surviving from ten to twelve hours. Patients who survived more than twelve hours displayed increasing numbers of ring forms and in survival periods from twelve to twenty four hours after injury, ring forms began to predominate. While these time relations probably do not apply strictly to cases of haemorrhagic encephalitis it is certain that these forms of bleeding are most numerous when the disease is of abrupt onset and of very short duration. In Baker's series of cases in 1935, where the lesions were almost exclusively haemorrhagic, five patients were found unconscious and death occurred within a few hours of the onset of the illness. Fulminating cases of this kind have also been reported more recently (Stephens; 1957 (case 1), Dunbar et al; 1958 (case 1)).

The literature of the third and fourth decades of the present century shows that the tendency to delimit various forms of encephalitis and to describe them as new disease entities persisted although with decreasing momentum. This was in part due to the recognition of closely similar morbid histological findings in encephalitis occurring in a wide variety of conditions. Greenfield (1930) was the first to give a /

a full account of the histological findings in two cases of encephalomyelitis following influenza although he qualifies the term "influenza" with inverted commas. Further cases of myelitis, encephalitis or encephalomyelitis following influenza were described by Liebers (1930), Rostan (1930), Grinker and Bassoe (1931), Greenfield (1950) and van Bogaert (1950). The morbid histological findings in Baker's (1935) cases of haemorrhagic encephalitis, moreover, would support a claim of influenzal aetiology in terms of reference obtaining in 1922, but, in fact, this author records clinical histories of prodromal upper respiratory infections in only a few of his cases. Conversely, Hurst (1941) described a form of acute haemorrhagic leuco-encephalitis as a previously undefined entity, but Crawford (1954), reviewing ten reports of this disease, pointed out that in seven cases the neurological signs were preceded by a prodromal period of upper respiratory infection of variable duration from two to fifteen days. As Crome (1954) notes in his review of this confused subject, cases similar to those of Hurst have been reported before; in addition to those included in the review by Adams et al.; (1949) there are the cases of Strümpell (1891), Straussler (1902) and Müller (1933). Encephalitis in these cases is often reported as following an illness resembling influenza, and this association has been recorded in subsequent and more recent reports (Southcott and Fowler, (1954); Kristiansen et al.; (1956); Rankin and Dance, (1956); and Aldridge, (1956)). The inference to be drawn from these observations is that some /

some cases reported as haemorrhagic encephalitis, influenzal encephalitis and acute haemorrhagic leuco-encephalitis were in fact variants of the same disease and this was the conclusion reached by Lhermitte (1950), Greenfield (1950) and Crome (1954). Both the fatal cases reported by Crome (1954) gave a history of a prodromal illness resembling influenza and both showed morbid histological features closely resembling those described by Hurst (1941). It is evident therefore that the scope of histological criteria for the diagnosis of influenzal encephalitis has been considerably widened since 1922.

The reaction of any patient to disease is modified by numerous factors and this variable response finds expression in the differences in the pathological and morbid histological findings in many cases, but whereas the range of pathological variation in some diseases is relatively small, and, in consequence, pathological diagnosis is more certain, in encephalitis the range is very wide, and because the total number of cases examined is relatively small, there is an appreciable latitude in the establishment of acceptable diagnostic criteria. At the present time, the principal features accepted in the morbid histology of influenzal encephalomyelitis are those of perivascular infiltration by lymphocytes or polymorphonuclear leucocytes often surrounded by areas of demyelination. Small focal haemorrhages are also common. Nerve cells are usually unaffected and this feature has /

has been the subject of comment by many authors. The lesions occur more often in the white matter of the brain than in the cortical ribbon or deep nuclear masses but in rare instances the grey matter is more severely affected than the white. The lesions may occur anywhere in the central nervous system and may be numerous or sparse. These changes, however, are not specific for encephalomyelitis following influenza. They are reported in association with the administration of anti-rabies serum (Babes and Mironesco; 1908), vaccination (Turnbull and McIntosh; 1926), bronchopneumonia (2 cases) chronic nephritis (2 cases) and one case each of acute rheumatic fever, pernicious anaemia, acute mitral endocarditis, secondary anaemia, cerebral haemorrhage, cerebral thrombosis and softening and meningovascular syphilis, (Alpers; 1928), smallpox (Troup and Hurst; 1930. Brouwer; 1931), rubella (Ferraro and Scheffer; 1931), chickenpox (Pette; 1936), atypical pneumonia (Perrone and Wright; 1943: van Bogaert; 1950) and they may occur in other conditions and may follow exposure to a variety of chemical substances and the administration of many therapeutic agents. More recently, experimental studies have shown that comparable lesions can be induced in monkeys by intramuscular injection of homologous brain emulsion (Kabat et al. 1946; Morgan 1946, 1947) and by the addition to this emulsion of Freund's adjuvants consisting of paraffin oil and killed tubercle bacilli. Kopeloff and Kopeloff (1947), Freund et al. (1947) and Alvard et al. (1948) were /

were able to induce similar lesions in guinea pigs, rabbits, mice and dogs on injection of the mixture.

These experiments mark an important departure in the history of studies on the pathogenesis of encephalitis for it had been shown for the first time that the lesions so often observed as the result of disease in man might be produced at will in the experimental animal by an antigen-antibody mechanism. Later investigations sought to eliminate inessentials and to isolate the antigen responsible for these changes. Terai (1955) produced allergic encephalitis in experimental rabbits by subcutaneous sensitizing doses of human cerebral white matter phosphatide followed by intravenous injection of the same material and Colover (1954) and Colover and Consden (1956) directed studies to the isolation of the active principle in the tubercle bacillus. Barlow (1956) discussed experimental findings of abnormal blood-brain permeability and elicited important observations with reference to the time relationships of changes in vascular permeability and demyelination. The implications of the original work of Kabat et al. (1946) as applied to human disease suggested an allergic mechanism in the pathogenesis of encephalitis and this view was further supported by the work of Ferraro et al. (1950) who showed that some measure of protection could be afforded to animals in these experiments by the previous injection of normal brain tissue. This was interpreted as the inhibiting effect of desensitization in the induction of experimental encephalitis. The publication of these results led /

led to reassessment of the pathogenesis of human encephalitis and some authorities now supported the view that this condition was of allergic aetiology (Crawford; 1954, Greenfield; 1956).

From the foregoing evidence it is clear that pathological changes in the central nervous system characteristic of encephalitis, in a broad sense, may arise in response to a wide variety of pathological or experimental processes. This is often interpreted in terms of the limited range of response open to a highly differentiated system, but since it has been shown that many causes may give rise to closely similar results, it is therefore improper to ascribe one such result to a particular cause. In this sense, no combination of morbid histological features in the central nervous system can be described exclusively as typical of influenzal encephalitis since encephalitis which may be associated with influenza can present with either haemorrhagic or perivascular inflammatory lesions in predominance and the nature of the morbid histological features in any particular case is probably modified by individual variation and is certainly modified by the duration of survival. On the other hand such wide divergencies in morbid histology are by no means characteristic of encephalitis lethargica and one of the most significant features in the history of this disease is the remarkable measure of agreement between the descriptions of the lesions found in cases from all parts of Europe and the New World. This fact alone gives rise to the suspicion that while /

while encephalitis lethargica is a disease related to influenza it is one whose mode of pathogenesis is constant and specific.

It is of value briefly to consider the morbid histological findings in encephalitis lethargica in the light of these later studies. In the Ministry of Health Report No. 11 (1922) MacNalty makes it clear that the descriptions given are those on which British and contemporary European authorities were agreed. The principal feature of the disease was a perivascular inflammatory lesion occurring about veins of medium or small size. The infiltrating cells included large and small lymphocytes and occasionally these were accompanied by plasma cells. Von Wiesener, whose observations were cited in the Report of 1922, also described aggregations of polymorphonuclear leucocytes in scattered areas. These lesions, often very numerous in the pons and in the basal nuclei, also occurred in any part of the brain stem or bulb. Neuroglial proliferation was described as forming foci in the upper pons in some cases. All observers found that changes in the spinal cord were either very slight or were entirely absent while those in the leptomeninges were of an insignificant cellular increase in the pia mater, particularly about blood vessels. There was general agreement that nerve cells in some cases displayed widespread alterations from slight chromolysis to complete atrophy. Lesions were slow in developing; Lereboullet and Hutinel, cited in the 1922 Report, described a case /

case coming to necropsy within a week with negative histological findings and MacNalty stated that cases surviving from three to ten days displayed little of note on microscopical examination.

The perivascular lesions in this description are identical with those found in very many other forms of encephalitis and this common response may indeed be determined by the limited powers of the central nervous systen to respond to various noxae. The site of the majority of the lesions, however, is significant; they were most numerous in the pons and basal nuclei. In the upper pons also, foci of neuroglial proliferation were described very frequently and this feature may represent a form of response to irritative lesions in this area. In contradistinction to the findings in other forms of influenzal encephalitis, nerve cells were affected in cases which survived for some weeks. The combination of these features suggests that in encephalitis lethargica the disease process is located, at least in the first instance, about the area of the pons, mid brain and basal nuclei and this concept accords well with the profound disturbance of the sensorium which is characteristically a presenting feature in clinical descriptions of the disease. Changes in the nerve cells, moreover, suggest that the disease process in some way operates electively within purely nervous tissue to the destruction of individual nerve cells and their fibres. These features contrast with those of haemorrhagic or perivenous encephalitis which /

which also may follow influenza. In these conditions, the cerebral vessels are again principally affected but the lesions are widespread in the white matter of the cerebral hemispheres and localisation in the brain stem is not a feature in these conditions. Furthermore, nerve cells are almost always unaffected. It seems probable, therefore, that encephalitis lethargica may be separated as a distinct entity from other forms of encephalitis which may arise after influenza. These latter forms comprise a large group with many variations in morbid histological detail and in default of clearer understanding it is necessary, at present, to relegate them to a group of allergic disorders of the central nervous system.

While it is difficult, in the light of historical considerations, to accept the belief that encephalitis lethargica was a new disease arising for the first time in Vienna in 1917, so also it is difficult to subscribe to the widespread impression that the disease has largely died out since the third decade of this century. Furthermore, it is unreasonable to suppose that the clinical and pathological features of any disease remain constant over long periods of time. It is commonplace that this is not so in many forms of infectious disease and there is some evidence to show that the clinical features of encephalitis lethargica have undergone considerable modifications within the comparatively short period of a decade. As early as 1921, Bramwell noted that the familiar clinical features of encephalitis lethargica, stupor /

stupor and inaccessibility, were apparently giving way to excitement, and in the outbreak in Liverpool in 1923 evidence of motor excitement was more common than lethargy or ocular palsy while similar changes also were evident in the symptomatology of the Sheffield outbreak of 1924 (Hall and Yates; 1926). In many instances in both the Liverpool and Sheffield outbreaks psychomotor symptoms were prominent. These changes in the clinical features of the disease show considerable variation from the general clinical picture built up as the result of experience in the 1918-19 epidemic. Within recent years there has been a tendency among those who still regard encephalitis lethargica as an extant disease to take the view that it has assumed a more benign and chronic form so that mild cases occur which are ambulant during the acute phase and in these instances, retrospective diagnosis is often aided by the appearance of chronic nervous disorder at a later date.

CHAPTER II

AETIOLOGY AND DIAGNOSIS

The eighteen cases which form the basis of this study fall into two groups. The first of these comprises cases 1 - 7, (A), inclusive and 8 - 10, (B), inclusive; all those presented as admissions to hospital in Greenock. The second group includes cases 11 and 12, (C), and cases 13 - 18, (D), inclusive; these presented either as hospital admissions in Glasgow and district or were traced as a result of a survey of virological and serological records available for examination in that city. The chronological order of occurrence is shown:-

Greenock cases			Glasgow cases		
Date	Case No.		Date	Case No.	
1957					
6. 8.57	1 (first admission)	(A)	27. 9.57	11	(C)
26. 8.57	2		30.10.57	12	
15.9 .57	3				
25. 9.57	4				
3.12.57	5				
1958					
10. 1.58	6		12. 7.58	13	(D)
			18. 7.58	14	
25. 1.58	7		20.10.58	15	
			2.11.58	16	
26. 1.58	1 (second admission)		20.11.58	17	
1959					
15. 3.59	8	(B)	23. 4.59	18	
13. 4.59	9				
6. 6.59	10				

The Greenock cases therefore fall into two groups. The first of these (cases 1 - 7, (A),) occurred in the autumn and winter of 1957-58 and is considered in relation to the influenza /

influenza epidemic current at that time. This group shows a progressive increase in the severity of the illnesses.

Case No.

1. (first admission).	Mild meningo-encephalitis, complete recovery.
2.	Mild meningo-encephalitis, complete recovery.
3.	Mild meningo-encephalitis. Prodromal upper respiratory infection. Complete recovery.
4.	Psychotic syndrome. Prodromal influenza. Recovery.
5.	Acute meningo-encephalitis. Fatal.
6.	Chronic fatal meningo-encephalitis. Prodromal influenza.
7.	Acute fatal meningo-encephalitis. Prodromal influenza.
1.(second admission).	Acute fatal meningo-encephalitis. Prodromal upper respiratory infection.

The second group (cases 8 - 10, (B),) occurred in Greenock fifteen months later in the spring and early summer. Although there was no recognised epidemic of influenza current in Renfrewshire in the spring of 1959, prodromal illnesses were present in cases 8 and 9 and these were diagnosed respectively as influenza and as an acute febrile illness of indeterminate nature. This group shows a progressive diminution in the severity of the illnesses.

Case No. /

Case No.

8.	Acute fatal encephalitis. Lesions principally in mid brain. Prodromal influenza.
9.	Acute meningo-encephalitis. Recovery with residual paresis.
10.	Acute meningo-encephalitis. Complete recovery.

The influenza pandemic of 1957 spread to Renfrewshire about the middle of September of that year and was, in part, introduced from Glasgow where the disease had already appeared. On 15.9.57 ships of the fleet of the North Atlantic Treaty Organisation anchored off Greenock with cases of influenza in the ships' companies. Two ratings suffering from this disease were admitted to an infectious diseases hospital in Greenock on 16.9.57 and the infection thus introduced spread swiftly among the nursing staff which was reduced from this cause to half strength by 1.10.57.

Further evidence in the spread of the epidemic in the community is afforded by statistics supplied by the Ministry of Labour and National Insurance which show that the average number of workers certified as unfit for work in this area because of illness of all kinds varies, as a general rule, from three to four hundred per week. The following list of weekly figures for September and October 1957 reflects the prevalence of influenza at this time and indicates the peak of the epidemic.

Number /

Number of workers in Greenock certified unfit because of illness:-

17. 9.57 600

24. 9.57 1762

1.10.57 4039

8.10.57 3688

15.10.57 1443

22.10.57 600

29.10.57 ..... 488.

Although the peak of the influenza epidemic was reached in West Renfrewshire early in October 1957, sporadic cases of acute respiratory illness, diagnosed as influenza, continued to occur in that county and in Argyllshire and Bute into the spring of 1958. The chronological relationship of cases 1 - 7, (A), comprising the initial outbreak of meningo-encephalitis at Greenock, to the peak of the influenza epidemic in that area, is shown in Fig. 1. Also included for comparison in the same connection are cases 11 and 12, (C), of the Glasgow group, since these are presented for their close clinical correspondence with case 4 (Greenock group)and because the influenza epidemic was still in progress in Glasgow at that time.

CHRONOLOGICAL RELATIONSHIP OF CASES
IN GROUPS A AND C WITH INFLUENZA
EPIDEMIC OF 1957.

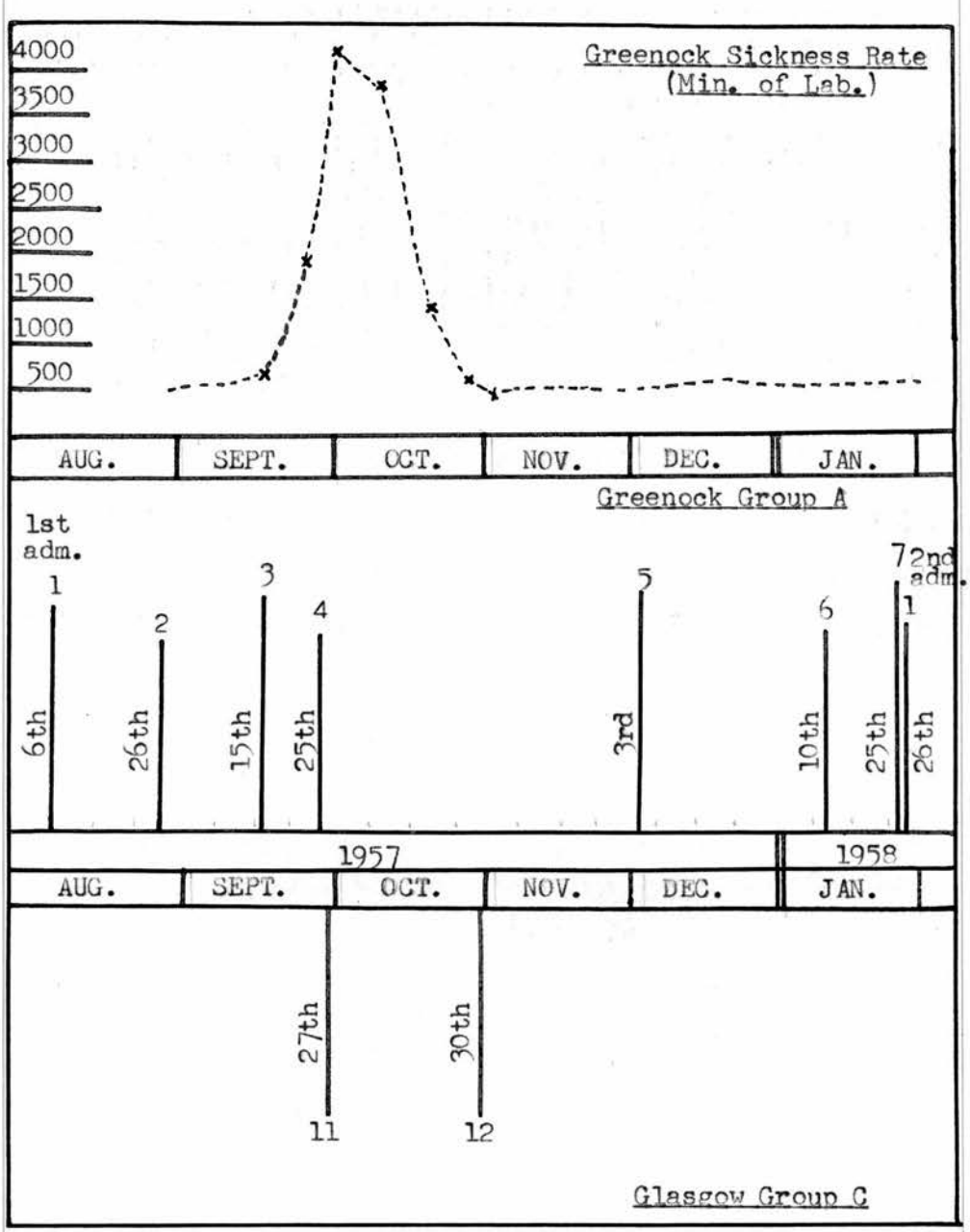

FIG 1

The group of hospitals at Greenock supplies medical services for that town and for Port Glasgow, Gourock and adjacent rural areas. Additional patients also are admitted from areas further afield both in Renfrewshire and Argyllshire. It is therefore impossible accurately to estimate the total population served by this hospital group but it exceeds one hundred thousand persons. The incidence of encephalitis in this population as estimated by a study of hospital records and returns of infectious diseases is as follows:-

	Age	Sex	Diagnosis	Result	No. of cases
1954	5	F	Unknown aetiology.	Discharged well	2
	24	M	Mumps encephalitis.	Discharged well	
1955	11	M	Poliomyelitis encephalitis.	Died	2
	30	M	Poliomyelitis encephalitis.	Died	
1956	-	-	-	-	-
1957	6	M	Mumps encephalitis.	Discharged well	2 (to end of April 1957).
	18	M	Mumps encephalitis.	Discharged well	

These figures are of the same order as those supplied by Greenfield (1950) and Conybeare (1956). The presentation therefore of four fatal cases of encephalitis (cases 5, 6, 7 and 1) of unknown aetiology within a period of eight weeks, the two latter occurring within a week, suggests the possibility of a common toxic or infectious agent as the exciting cause.

Cases /

Cases 11 - 18 are listed as the Glasgow group because either they presented at hospitals in the city area or were traced after inspection of virological and serological records available there. These cases are further divided into two groups.

The first, (C), comprises cases 11 and 12 which are included because they are examples of moderately severe illnesses presenting as psychotic syndromes with recovery in two adolescent males following attacks of influenza in each case. Both cases are closely comparable with case 4 in the Greenock group and occurred at about the same time.

The second group, (D), comprises cases 13 - 18. All these cases were traced after a survey had been made of the virological and serological records in the Department of Virology at Ruchill Hospital, Glasgow. The minimum criterion of selection was of a fourfold rise or fall in titre in the herpes complement fixation test during the period of illness. Inquiries about patients traced in this way were made at the clinical units from which the serological specimens originally had been submitted and where possible clinical and pathological examinations were carried out. The patients in cases 13 - 16, inclusive, were infants from six to fourteen months old.

Case No.

13. Acute meningo-encephalitis with signs of upper respiratory infection. Recovery with residual paresis.

14. Acute meningo-encephalitis with signs of upper respiratory infection. Rapid and complete recovery.

15. /

Case No.

15. Fatal acute meingo-encephalitis with signs of upper respiratory infection.

16. Acute meningo-encephalitis with signs of upper respiratory infection. Complete recovery.

The remaining two patients, in cases 17 and 18 were adults.

Case No.

17. Acute meingo-encephalitis. Prodromal febrile illness. Partial recovery.

18. Chronic myelitis. Prodromal influenza. Partial recovery.

The patients in cases 1 - 6 and 8 - 10 inclusive, were resident in the urban area of Greenock and Port Glasgow. The patient in case 7 was resident at Dunoon but was admitted to hospital in Greenock. The patients in cases 11 and 12 were resident in widely separated areas of the city of Glasgow and these were admitted to different institutions within the city between October 1957 and March 1958. The patient in case 13 was resident in a rural district of Angus and was admitted to hospital in Dundee. The patients in cases 14 - 17 inclusive were resident in various districts within the Glasgow area and the patient in case 18 was resident in Lanarkshire. Scrutiny of the records and specific enquiry showed that none of the patients had any social contact with any of the others nor was any social relation found between any of the families concerned. These findings held good within the Greenock group and within the Glasgow group and between the two groups. Each patient /

patient presented as a single example of a particular illness within a family or group of families resident as neighbours or as isolated cases in an institution (case 2) or ship's company (case 3). Enquiries at places of work or education failed to disclose the occurrence of any similar cases in those in daily contact with any of the patients. Even those patients in intimate daily contact with others, as children sharing the same bed and the same classroom, or husband and wife, were found to be solitary examples of this particular illness.

None of the patients in the present series had been recently vaccinated or immunised and none had suffered from exanthemata shortly before the onset of illness. Specific enquiries failed to implicate drugs, chemicals or dietary elements as possible aetiological factors. Bacteriological studies were uniformly negative and in one case only (case 7) was a virus identified in specimens of brain at necropsy in a concentration which appeared to exclude the possibilities of contamination or symbiosis. All virological investigations made on other necropsy specimens were negative.

All cases presented are considered individually in the following pages with reference to aetiology and diagnosis.

Case 1. /

Case 1. Female. Age: 20 years. (6.8.57; first admission).

The patient complained of the abrupt onset of intense frontal headache accompanied by nausea. Admitted to hospital she began to improve and was discharged well.

Duration: 2 days.

(26.1.58; second admission).

The patient complained of the onset of intense headache following a severe cold. The next day she developed right sided facial paresis, and, five days later, a right sided hemiparesis. The patient deteriorated steadily and died.

Duration: 7 days.

In this case, the diagnosis, based on pathological findings, is of acute haemorrhagic leucoencephalitis. The pathological appearances closely resembled those associated with the description given by Hurst (1941) although demyelination, which Hurst regarded as an important factor, is not conspicuous in the morbid histology.

An unusual and probably important feature in the aetiology is the history of two illnesses separated by a period of five months. The patient was admitted to hospital early in August 1957 complaining of severe headache and nausea and the same clinical syndrome ushered in the fatal illness of January 1958. The absence of any prodromata and the abrupt onset of pain in the first illness do not support the view that the disturbance was related to infection. Examination of the cerebrospinal fluid at this time (6.8.57) gave normal findings, but further studies on the cerebrospinal fluid were not made because the patient recovered within two days. A long history of dysmenorrhoea, for which the patient had earlier been referred for gynaecological opinion, suggested that

she /

she might have had recourse to some therapeutic agent unknown to her medical attendant. This suggestion was explored as far as possible, with negative results. The association of menstruation and the onset of encephalitis has been observed previously (Stephens; case 2; 1957) but its significance, if any, is not known.

The prodromata of the fatal illness in January 1958 were those of upper respiratory infection which may have been influenzal as many cases of this disease were still occurring sporadically in the district at the time. Post influenzal encephalitis may present pathological features similar to those seen in this case although rarely of comparable severity, but an influenzal aetiology for the fatal illness in January suggests that the episode in August does not bear a close relationship to the cause of death. It seems probable that there is an allergic component in the aetiology of this case and the features of the morbid histological findings lend support to this view. The nature of the sensitising antigen howevere remains unknown.

Case 2. Female. Age:20 years. (26.8.57).

The patient, who was six months pregnant, complained of stiffness and pain in the back of the neck accompanied intermittently by vomiting. The pain persisted for four days and spread to the vertex. After admission to hospital the patient improved steadily and was discharged well. Duration : 15 days.

Three weeks after the first admission of case 1, this patient /

patient was admitted to hospital with a complaint of severe headache and nausea accompanied by intermittent vomiting. The symptom complex is the same as that in case 1 (first admission) but is more severe. This patient was a Borstal inmate and was therefore not exposed to the same risk of infection as was an individual at large. Other cases of a similar nature were not reported from this institution about the same time. The patient was six months pregnant at the time of admission but her illness could not be related in any way to pregnancy. Clinical examination and laboratory findings were essentially normal but this patient was slower in recovering than was the patient in case 1, and was free of symptoms only after five days.

Case 3. Male. Age: 24 years. (15.9.57).

The patient complained of severe frontal headache, cough and malaise with signs of nuchal rigidity and positive Kernig's sign. He improved steadily in hospital and was discharged well.

Duration : 6 days.

Three weeks after case 2 this patient was admitted to hospital complaining of severe frontal headache. Nausea and vomiting were not presenting features but there was evidence of respiratory infection and of meningeal irritation. Recovery was rapid and the patient was free of symptoms within three days.

The nature of the three illnesses (case 1 (first admission), case 2 and case 3) is obscure and the rapid course and recovery in each instance did not promote extended studies /

studies or suggest, at that time, the desirability of further investigation. These three cases have many features in common and to relate each to the others would imply a disease process common to all giving rise to transient vascular disturbance in the central nervous system or its related membranes.

Case 4. Male. Age : 15 years. (25.9.57).

Following an acute febrile illness diagnosed clinically as influenza the patient developed severe headache and nausea followed by disorders of behaviour, salivation and vision. After admission to hospital he improved and was later transferred to psychiatric care and was subsequently discharged well.

Duration : 31 days.

This patient presented at hospital on 17.9.57 when the influenza epidemic in the area was of increasing severity. The behaviour disorders which followed the patient's influenzal illness did not conform to any pattern of mental illness and psychiatric opinion subsequently favoured a diagnosis of encephalitis. The clinical history in this case is typical of organic nervous disorder and the combination of diplopia and excessive salivation point to irritative lesions in the floor of the fourth ventricle. Diplopia was transient but excessive salivation persisted for several weeks. An acute phase of disordered behaviour was characterised by aggressive and uninhibited tendencies of which the patient had subsequently little recollection.

Case 5. Male. Age : 17 years. (3.12.57).

The patient complained of severe frontal headache and general malaise accompanied by nausea and vomiting. After admission to hospital he developed a right facial palsy and Jacksonian seizures with spasticity. He continued to deteriorate and died.

Duration : 9 days.

The /

The patient was a youth who sought medical advice because of a severe headache accompanied by nausea. It was not possible to elicit any history of upper respiratory infection either preceding the headache or contemporary with it. In the course of the fatal illness which lasted nine days, facial hemiparesis presented on the second day. Thereafter, the signs of nervous lesions became generalised and were not confined to one side of the body. Retention of urine which developed on the fifth day of the illness raised the possibility of localisation of lesions in the lumbar segments of the spinal cord although this was not confirmed at necropsy.

At necropsy the morbid anatomical findings in the brain were those of encephalitis. Morbid histological studies confirmed the diagnosis of perivenous meningo-:encephalitis and the appearances in this case more closely resembled those of case 7 than those of case 1. Plasma cells however were present in the meningeal exudate but were not seen in case 7. With this exception, the lesions in the brain in cases 5 and 7 were closely comparable although the vascular lesions, on the whole, were less profuse and less severe than in case 7.

Basal pulmonary congestion and oedema had been noted at necropsy but examination of sections from the affected areas of the lungs disclosed the presence of foci of bronchopneumonia associated with areas of haemorrhage. These /

These findings were similar to those seen in influenzal bronchopneumonia but were less severe.

There is insufficient evidence in this case to allow of more specific diagnosis than that of perivenous meningo-encephalitis. The previous history of atypical pneumonia, fifteen months before the onset of the fatal illness, is interesting since this condition is sometimes followed by encephalomyelitis. Bornstein and Efrati (1955) reported a case also of a youth of seventeen years of age who developed encephalomyelitis after atypical pneumonia. In their case, however, although the patient was still alive one year after the onset of the disease, neurological signs had become evident within three weeks of the beginning of the illness. The interval of fifteen months in case 5 without symptoms leads to the conclusion that the attack of pneumonia in September 1957 cannot be implicated in the aetiology of the final illness.

Case 6. Male. Age : 6 years. (10.1.58).

The patient had a febrile illness, diagnosed clinically as influenza, in October 1957. After his return to school progressive deterioration in his mental state was noted. In January 1958, the patient developed restlessness, irritability and purposeless movements of the limbs. After admission to hospital he continued to deteriorate with development of spasticity and inaccessibility. He died after transfer to an institution for chronic disorders. Duration : 9 months.

The patient in this case was a male child six years of age whose illness was of insidious onset. Permission for necropsy was not obtained and the diagnosis and differential /

differential diagnosis is therefore based upon clinical and laboratory findings and the correspondence of these results with those reported by others in similar cases.

The disease is regarded as the slow development of dementia and the advance of an irreversible process of destruction within the central nervous system. These are the features of subacute sclerosing leucoencephalitis described by van Bogaert and de Busscher before the Neurological Society of Paris in 1939 and the present case has many features in common with those described by these authors. Since the date of these authors' communication, however, many contributions to the literature have disclosed the existence of a large group of subacute sclerosing encephalitides. Attempts to classify these diseases on the basis of history and clinical findings (Lebascle; 1956) are not convincing, nor is there wide agreement that minor differences in morbid histology are diagnostic of separate disease entities. Kalm (1952), however, on the basis of pathological findings, regards panencephalitis of Pette and Doring, subacute sclerosing leucoencephalitis of van Bogaert and inclusion body encephalitis of Dawson as diseases at least of similar origin. In a series of twelve cases from Frankfurt am Main, Krücke (1957) describes acute, subacute and chronic relapsing encephalitis with inclusion bodes in patients of varying age from eleven months to sixty two years. The lesions /

lesions here affected mainly the cerebral cortex, the cerebellum being spared, but necrotizing changes were also apparent in the spinal cord. Inclusion bodies which resembled those of herpes simplex encephalitis were seen mainly in the frontal and temporal lobes, including the insula and also in the cingulate gyrus. The author suggests that further clinical, pathological and virological studies are required in this group of cases. It is evident that these limitations have been widely appreciated and in an attempt to widen the terms of reference from the clinical angle, careful electroencephalographic studies have been made in many cases (Foley and Williams; 1953, d'Avignon et al; 1954, Barbier; 1955, Lesbascle; 1956, Hamoen et al.; 1956, Recordier et al.;1956, Nayrac et al.; 1957) although firm diagnostic criteria have not emerged.

In the present case it was not possible to carry out studies in electroencephalography and the findings on examination of the cerebrospinal fluid, while characteristic, are not referable to a particular variety of chronic encephalitis. Virological studies were negative.

With regard to a possible aetiological factor in this group of diseases it is only in recent years that it has been suspected that a virus infection of the nervous system can produce a chronic or subacute progressive condition. A significant experimental series inducing chronic encephalomyelitis in hens by injection of a virus obtained /

obtained in human cases of encephalomyelitis, was reported in 1951 by Margulis et al. Recently, van Bogaert has reproduced subacute encephalitis in rhesus monkey by intracerebral inoculation of material obtained at necropsy from the cerebral hemispheres of a human case of subacute sclerosing leucoencephalitis. Successful induction of the disease in experimental animals was effected with greater certainty when the inoculum was not subjected to deep-freezing (van Bogaert; 1958). The illness in this patient (case 6) developed immediately after an attack of influenza and this may be of significance in the light of foregoing results.

Case 7. Male. Age : 33 years. (25.1.58)

About 20.1.58 the patient complained of an illness clinically diagnosed as influenza. Five days later he developed persistent headache with shivering and malaise. After admission to hospital (30.1.58) he became comatose and deteriorated steadily until death four days later. Duration : 9 days.

The onset of an illness resembling influenza ten days before the patient was admitted to hospital is an important feature in the history of this case. The respiratory infection was made worse by exposure to rain although it is interesting in this connection to note that death from cerebral purpura has been recorded, although /

although very rarely, after such an isolated event. The patient was moribund on admission to hospital and in these circumstances clinical examination did not yield any information of value in the localisation of the disease process.

The single examination of cerebrospinal fluid made on the day of admission disclosed the presence of fifty two cells per cubic millimetre and most of these were polymorpho-:nuclear leucocytes. The total protein content was not appreciably raised but the sugar level of ninety one milligrams per cent was high. The white cell count in the blood was normal but a high blood urea indicated failing renal function.

The morbid anatomical findings at necropsy were unequivocally those of acute encephalitis and the morbid histological findings were characteristic of acute perivenous meningoencephalitis. It was evident as sections were examined from the spinal cord, medulla and pons that the lesions, largely absent in the spinal cord, became progressively more severe at ascending levels in the brain stem. The mid brain was submitted, along with specimens from the cerebral cortex, pons, medulla and spinal cord for virological examination and a virus, (414/58) identified as herpes simplex, was isolated from the mid brain. However, the macroscopic appearances and the morbid histological findings in the brain in case 7 did not resemble those of acute /

acute herpetic encephalitis. The gross characteristics of this disease are commonly those of massive encephalomalacia (Smith et al.; 1941, Zarafonetis et al.; 1944, Whitman et al.; 1946, Wildi; 1951, France and Wilmers; 1953, Greenfield; 1958) and the morbid histological features include phagocytosis of degenerating myelin, necrosis, and the presence of very numerous acidophil inclusion bodies within both glial and neural nuclei. In acute herpetic encephalitis also, the seat of the most severe lesions is in the cerebral hemispheres but inflammatory lesions have also been observed occasionally in the basal ganglia and in the brain stem. It has been found possible in many cases to isolate the herpes simplex virus from the cerebral cortex. The distribution of the lesions within the central nervous system in this patient (case 7) did not resemble this description nor was it possible to isolate a virus from the tissues of the cerebral hemispheres.

The clinical and pathological features of case 7 resemble many descriptions of encephalitis lethargica.

Case 8. Female. Age : 5 years. (5.3.59)

Three days before the onset of neurological signs the patient had developed a febrile illness clinically diagnosed as influenza. She was found unconscious in bed (5.3.59) with generalised muscular twitching. On admission to hospital the child was deeply comatose with generalised spasticity. Death occurred eight hours after admission.

Duration : 24 hours.

The /

The clinical diagnosis of influenza in this case was confirmed by the isolation of Type A influenza virus from portions of lung obtained at necropsy.

The striking feature in the morbid anatomy of the central nervous system was the intense concentration of haemorrhagic lesions within a narrow zone centred about the pons. These features suggested an acute infantile encephalopathy due to venous thrombosis or thrombophlebitis, the anatomical substrate of which is haemorrhagic infarction with oedema (van Bogaert; 1959). A search for thrombotic lesions in the larger arteries and veins of the affected area, was, however, without result. Microscopic examination disclosed that many small vessels, presumably venules, at the centres of haemorrhages in the pons showed thrombi (Fig. 5), but these changes may be interpreted as end results of perivenous inflammatory and necrotic lesions exemplified at an earlier stage in Fig. (6). Such perivenous lesions are indistinguishable from those encountered in perivenous leucoencephalitis of undoubted infectious aetiology. While there is no doubt that stasis and thrombosis are important, and probably essential, preliminary mechanisms in the production of petechial haemorrhage in the central nervous system, it is generally agreed that these changes are due to specific pathological alterations in the walls of /

of the vessels rather than to alterations in the fluid composition of the circulating blood secondary to fever and dehydration. The great predominance both in severity and numbers of haemorrhagic over other forms of vascular lesions was not unexpected in view of the very short period between the onset of neurological signs and death. Reference has been made already to earlier findings on this topic. But while it was for some time generally accepted that the lesions in influenzal encephalitis were haemorrhagic in nautre, at the same time, they were recognised as being widely distributed in the brain although more numerous in the white than in the grey matter. It has not proved possible to find any description of influenzal encephalitis with the very localised distribution characteristic of this case. The degree of localisation of the haemorrhagic lesions appeared also to eliminate the possibility of an allergic aetiology.

If this disease resulted from the direct invasion of the central nervous system by a virus the distribution of the lesions again does not suggest that the agent gained entry by way of the blood stream. A neurotropic agent gaining access to the pons might give rise to acute and rapidly fatal lesions. However, inclusion bodies were not seen anywhere in sections prepared from the pons or elsewhere in the brain. Similarly, attempts

to /

to isolate a virus from all specimens of the central nervous system obtained at necropsy were uniformly negative.

The short survival period of this patient did not permit serological investigations to be carried out.

Case 9. Male. Age : 4½ years. (13.4.59)

The patient became ill with anorexia, sweating and irritability followed by convulsions. On admission to hospital he was comatose with Jacksonian seizures of the left side of the body. His general condition improved slowly but a flaccid paralysis of the left side of the body developed subsequently. At the date of his discharge (16.6.59) he still had residual paresis of left arm and leg.

Duration : 64 days.

This patient recovered from an attack of measles eight weeks before the development of the florid neurological syndrome and this interval is regarded as being too long to permit a diagnosis of post-exanthematous encephalitis. The history of intermittent twitching of the left arm in the weeks before admission to hospital is characteristic of motor fits of Jacksonian type. Such motor disorders are widely regarded as expressions of neuronal anoxia resulting from venous engorgement and oedema of the motor cortex whether following infection or trauma.

The /

The evidence of the carotid angiogram and of the ventriculogram, four and eight days respectively after admission to hospital support the localisation of the morbid process within the right cerebral hemisphere. It seems probable that the relief of intracranial tension effected by ventriculography was itself of therapeutic moment since the patient began markedly to improve almost at once. The persistence of left sided paresis, however, suggests that some neurones succumbed during the acute phase of the disorder and it is possible that thrombotic or haemorrhagic sequelae may have followed the acute disturbance.

The slow evolution of the illness suggests a steadily developing inflammatory lesions with subsequent resolution of the acute process, but the evidence in this case for diagnosis and aetiology is meagre despite extensive investigation.

The diagnosis, therefore, of perivenous encephalitis, possibly complicated by thrombosis or local haemorrhage is made in this case although the serology does not indicate any specific agent.

Case 10. Male. Age : 15 years. (6.6.59)

The patient complained of the abrupt onset of severe pain at the back of the head and of feverishness later accompanied by vomiting. He was admitted to hospital and became drowsy, confused and irritable. His condition improved gradually and he was discharged well.

Duration : 50 days.

The /

The abrupt onset of the febrile illness in this case was accompanied from the start by signs of meningeal irritation and although this was marked by the third day of the illness at no time was there any evidence that the brain itself had become the seat of infection. The drowsy and irritable state of the patient on the day after admission is interpreted as a general reaction to the infection. Although the level of sugar in the cerebrospinal fluid was raised at this time, the cell count, chloride and protein levels were always within normal limits.

The identification of Coxsackie A virus in the stool of this patient (16.6.59) indicates a probable diagnosis in this case of mild aseptic meningitis due to this organism.

Case 11. Male. Age : 15½ years. (27.9.57)

In late September 1957 the patient had an acute febrile respiratory illness clinically diagnosed as influenza. On 25.9.57 the patient exhibited disordered behaviour for which he was referred to hospital on 27.9.57. He was drowsy, irritable and aggressive. He improved steadily and was discharged well.

Duration : 11 days.

The family history of febrile respiratory illness and the current state of epidemic influenza make it probable that the /

the clinical diagnosis of influenza was correct in this case. As in case 4, the onset of the psychotic syndrome was preceded by a severe headache and a period of somnolence. Thereafter the patient's behaviour became aggressive and uninhibited. A close similarity with the course of events in case 4 is apparent. In this case, however, diplopia and excessive salivation were not presenting symptoms although the patient experienced visual hallucinations.

The aggressive attitude in the patient was pronounced soon after his admission to hospital although it was evident only when he was disturbed. After a few days the patient improved rapidly and was discharged well within eleven days.

Laboratory and other investigations in this case were uninformative.

Case 12. Male. Age : 15 years. (1.10.57)

The patient showed disordered behaviour over a period of nine days after an acute febrile illness clinically diagnosed as influenza. Two further episodes of disordered behaviour of similar duration subsequently followed a sore throat and an attack of toothache. The patient was not admitted to hospital and the illness resolved with treatment at home.

Duration : 30 days.

As in cases 4 and 11 the circumstances attending the onset of febrile respiratory illness in this patient in October 1957 tend to confirm the diagnosis of influenza which preceded the psychotic syndrome. The elements of withdrawal and /

and a partial inaccessibility are more prominent features in this history. After the initial phase of delirium, the recurrent episodes of illness were typically attended by somnolence and the patient lost all sense of time while so affected and was unable to remember these intervals on recovery.

This patient was not admitted to hospital with the result that laboratory investigations were not made. Psychiatric opinion at the child guidance clinic to which the patient was referred favoured a diagnosis of mild encephalitis as the basis of the psychotic disorder.

The last six cases in the present series (cases 13 - 18 inclusive) were investigated retrospectively after examination of serological records in the virology laboratory. The minimum criterion of selection was a fourfold rise or fall in titre in the herpes simplex complement fixation test during the period of illness.

Case 13. Male. Age : 1 year 2 months. (12.7.58)

The patient was admitted to hospital because of vomiting, irritability and convulsions. Neck rigidity and a left sided extensor plantar reflex were present. He recovered and was discharged well on 6.8.58. He was readmitted on 11.8.58 with hyperpyrexia and hyperkinesia. The patient improved slowly and was discharged with residual disability on 14.10.58.

Duration : 94 days.

In this case the clinical findings on admission in the first illness (12.7.58 - 6.8.58) were those of upper respiratory inflammation /

inflammation with catarrhal tonsillitis and ulceration of the palate. The neurological signs were of meningeal irritation and impairment of motor function.

Serial investigations of the cerebrospinal fluid from 12.7.58 - 18.7.58 showed a steady rise in the number of cells present and a parallel increase in total protein content. Over the same period a high initial level of sugar (145 mgm%), fell to a level within normal limits. Eight days after admission the patient showed an abrupt clinical improvement and this was steadily maintained until discharge to convalescence on 6.8.58. At this time the patient appeared well and was walking normally. During this first illness, serological studies for herpes simplex antibody showed a titre of 128 (17.7.58). This is a high level in itself for a patient without clinical evidence or recent history of herpetic infection. Three weeks later, however, the titre had risen to 1024 (7.8.58) and this is an eight-fold increase within a period of twenty one days. It is difficult to avoid the conclusion that herpes simplex was the active agent in this neurological disorder.

The development of earache in the interval between the two phases of illness is of interest in the differential diagnosis of the second phase since it raises the question of otitic hydrocephalus. In this condition important signs are those of sixth cranial nerve palsy and papilloedema and while the pressure of the cerebrospinal fluid is commonly raised, it shows /

shows no appreciable increase in cell or protein content. The chief clinical feature at the second admission was of hyperkinesis which made detailed clinical examination difficult. The records at this time do not yield information with respect to the state of the ears, presence of strabismus or the pressure of the cerebrospinal fluid. The cell count in the cerebrospinal fluid, however, was of twenty lymphocytes per cubic millilitre and seventy three milligrams of protein per hundred millilitres; these findings do not support a possible diagnosis of otitic hydrocephalus. In contrast, the comparison of the high sugar level at the beginning of the first phase (145 mgm%; 12.7.58) with the comparatively normal level at the beginning of the second phase (63 mgm%; 11.8.58) is noteworthy.

The patient deteriorated rapidly with increasing pyrexia and was transferred in extremis on 15.8.58 with a hyperpyrexia of 108.2°F. This finding suggests that the temperature regulating mechanism had been affected by a downward extension of the disease process in the brain stem.

The electroencephalographic findings in the period of convalescence from the second phase of the illness are compatible with widespread inflammatory changes in both cerebral hemispheres.

Case 14. Female. Age : 11 months. (18.7.58)

The patient was admitted to hospital because of listlessness and upper respiratory infection with nuchal rigidity. The condition resolved and the patient was discharged well on 4.8.58.

Duration : 17 days.

In /

In this case there is a history of upper respiratory infection present five days before admission to hospital and at admission the pharynx was inflamed and there were scattered rhonchi in both lungs. The positive neurological signs were slight but the general condition suggested a clinical diagnosis of non-paralytic poliomyelitis.

The diagnosis in this case again rests upon the rising titre in herpes antibody complement fixation test. The level of 4 at admission is regarded as a low normal, but the thirty-two fold increase during the ensuing period of eleven days indicates the identity of the active agent.

On clinical grounds it appears that the intracranial lesion was confined to a mild meningitic irritation which resolved completely within a week.

Case 15. Female. Age : 6 months. (20.10.58)

The patient was admitted to hospital because of anorexia, vomiting and listlessness followed later by signs of meningismus and convulsions. Spasticity developed and the patient died three weeks after the onset of symptoms. Duration : 22 days.

The fatal illness in this case was ushered in by an abrupt attack of vomiting followed by listlessness and anorexia. At admission, moderate inflammatory changes were noted in the upper respiratory tract. Bulging of the anterior fontanelle gave clear evidence of raised intracranial tension. The only pathological change in the cerebrospinal fluid was the finding

of /

of thirty cells per cubic millimetre. Four days after admission a spastic quadriplegia was established and the patient survived a further week with evidence of slight improvement followed by rapid collapse and death.

In this case the titre of herpes antibody in the complement fixation test was 16 on the day after admission; nine days later the titre showed a thirty-two fold increase.

In view of the accepted features of the morbid anatomy of acute herpetic encephalitis to which brief reference has been made already, the findings at necropsy and the morbid histological appearances are of interest. In terms of the macroscopic appearances of acute herpetic encephalitis as described by Smith et al.; 1941, Zarafonetis et al.; 1944, Whitman et al.; 1946, Wildi; 1951, France and Wilmers; 1953 and van Bogaert; 1959, the appearances in this case correspond very well, with the exception that no large areas of softening in depth were present. The encephalomalacia here was confined throughout to cortex, and the medulla although severely affected, had not yet undergone massive disintegration (Figs. 1 - 4). These authors, however, were able to isolate herpes simplex with ease from specimens of brain obtained at necropsy. But in the present case no cytopathological agent of any kind could be isolated from specimens of the cerebral hemispheres, pons or medulla. This negative finding is more striking because this patient died in the same hospital which houses also the area virology laboratory and, in the expectation /

expectation of positive virological findings, material was transferred from the post mortem room to the virologist with minimum delay. Moreover, necropsy was carried out within two hours of death.

A prominent feature in the morbid histology of the cases described by the authors quoted above was the prevalence in tissue cells of very numerous acidophil intranuclear inclusion bodies. No such appearances were seen in any of the sections examined from the present case. Only in the pons was there minor evidence of margination of nuclear chromatin in the nerve cells (Fig. 8) and this was unaccompanied by intranuclear inclusions.

This case is regarded as one of acute herpetic encephalitis on serological and morbid anatomical evidence. The failure to isolate herpes simplex is of particular significance when considered in the light of the favourable circumstances obtaining.

Case 16. Male. Age : 9 months. (2.11.58)

The patient was admitted to hospital because of anorexia, listlessness and vomiting followed by coma and convulsions alternating with spasticity. The patient improved with treatment and was discharged well on 17.11.58.

Duration : 15 days.

The prodromata in this case were of listlessness, anorexia and vomiting, but on admission moderate inflammatory changes were noted in the pharynx and scattered rhonchi were present in both lung fields. In this case also there is evidence, therefore /

therefore, of respiratory infection which probably preceded the onset of neurological signs. The history of intermittent vomiting followed by convulsions alternating with flaccidity suggest raised intracranial tension although the state of the anterior fontanelle is not recorded. The cerebrospinal fluid on the day after admission showed a slight increase in the number of cells (12 per cu.mm.) but the sugar content was high (127 mgm%). Three days later the cells had increased fourfold but the sugar content was halved.

The diagnosis in this case rests upon an eightfold increase in the titre of the complement fixation test for herpes simplex. This increase appears over a period of three weeks. It is of note that this patient was treated by exhibition of eucortone together with oxygen and penicillin. Although this patient was never as seriously ill as the patient in case 12 both showed a remarkable degree of recovery and both were treated by corticoid therapy. The findings in this case suggest that the disorder was, in fact, a meningitis or meningo-encephalitis of moderate severity due to herpes simplex.

An interesting feature in this case and one which was encountered also in cases 7 and 17 is the appearance of a transient punctate erythematous rash in the skin. This feature has previously been noted in clinical descriptions of acute herpetic encephalitis and encephalitis lethargica but presumably because no bullae were formed, no record is known of attempts to isolate a virus from these lesions.

Case /

Case 17. Female. Age : 46 years. (20.11.58)

The patient was admitted to hospital in status epilepticus following an undiagnosed febrile illness. The patient improved with treatment and was discharged with residual psychiatric disability on 17.1.59.

Duration : 58 days.

An interesting feature in the previous history in this case is the record of a stuporose disorder complicating influenza in 1956 but the patient recovered quickly on this occasion. A febrile illness with severe headache developed in this patient nine days before unequivocal neurological signs were established in the present illness. Subsequently the principal feature of the illness was a level of coma from which the patient could respond only to very painful stimuli. The absence of papilloedema and the presence of moderate nuchal rigidity suggest that although some meningeal irritation had developed, the intracranial tension was not greatly increased. The generalised macular rash on the trunk and limbs faded gradually a week after admission but did not become bullous.

Examination of the cerebrospinal fluid gave essentially normal findings although the sugar level was not estimated. The blood sugar was raised on admission and serum potassium was low, but within a week these readings were improving. Virological examination was negative except that the titre in the herpes simplex complement fixation test showed a fourfold increase over a period of a fortnight. The electroencephalo-:graphic findings were suggestive of encephalitis.

Case /

Case 18. Male. Age : 58 years. (23.4.59)

The patient was admitted to hospital with a complaint of numbness and paresis of both lower limbs, left shoulder pain and paresis of left arm following a febrile illness clinically diagnosed as influenza. He gradually improved and was discharged with residual neurological disability.

Duration : 5 months.

In this case there is a history of minor rigor and malaise occurring fourteen days before admission to hospital. The clinical diagnosis at the time was one of influenza.

A week after his initial disorder the patient began slowly to develop neurological signs. The most striking feature in the symptom complex is the unimpairment of consciousness and of the higher mental functions. The localisation of the disease process seems likely to have been in the lower cervical and upper thoracic portions of the spinal cord, although the region affected is not clearly defined. The flaccid paresis of the left arm and the subsequent muscular atrophy of this limb suggests a lesion involving anterior horn cells below the level C.5 on the left side. The severe sensory loss on the right side of the body up to the level of T.9 may indicate that a proportion of the sensory afferent fibres after crossing had been involved in the same process. The paresis of the right leg, however, was spastic and suggested an upper motor neurone lesion and this gains confirmation from the relative lack of wasting in the musculature of the right side. It therefore appears that the lesion might have been largely of the left side of the cord in the lower cervical segment and to have affected /

affected the lateral cortico-spinal tract at a lower level. The symptomatology as a whole, however, does not permit a narrow anatomical localisation of the lesion since the deep tendon reflexes were present on both sides and were, in general, more brisk on the left side of the body than on the right. Similarly, the upper motor neurone facial paresis of the right side noted on admission indicates involvement of the seventh nerve fibres between the nucleus and the geniculate ganglion; the probability here is that the nucleus itself was partially affected by the disease process which subsequently extended caudally to involve the cervical and thoracic portions of the spinal cord.

The relatively slow development of neurological dysfunction, its incomplete nature and its slow and patchy resolution, all suggest the activity of an infective agent spreading gradually in the nervous tissues and giving rise to temporary functional incapacity rather than to neuronal destruction and irreversible disability. In this case, the exposition of the process was displayed in paresis, paraesthesia and sensory loss with ultimate recovery. Similarly in case 16, a gradual development is evident but is here expressed in terms of loss of consciousness, epileptiform seizures and hypertonia and again is followed by gradual and partial recovery.

The only evidence of the identity of the infective agent in the present case is provided by the titres shown in the complement /

complement fixation test for herpes simplex. The level of 64 on the second day after admission is moderately high, but the fall to <4 within the subsequent period of forty-four days is strongly suggestive of recent herpetic infection. It is of interest that the complement fixation titre had fallen to levels currently accepted as normal within six weeks of admission to hospital. None the less, the clinical history indicates an active but slow pathological process persisting in the spinal cord long after this date. If a virus, in this instance, had been spreading from cell to cell by neuronal transmission within the spinal cord it would be unlikely to excite an antibody response in the serum and such a mode of progression would also explain the slow evolution of new clinical signs. In the absence of any herpetic skin lesions in the patient both before and during the present illness, a diagnosis of diffuse herpetic myelitis is proposed for this case.

CHAPTER III

VIROLOGY

The commonest form of primary herpetic infection in man is that of gingivo-stomatitis and this is generally acquired in childhood. A study of the distribution of the complement fixation herpes antibody in different age-groups by Holzel et al. (1953) has shown that although primary herpatic infection occurs predominantly in children, it is found also in adults. Individuals who acquire a primary infection develop antibodies to herpes simplex which persist for many years and they carry the virus for life. It is common knowledge that such persons are subject to recurrent attacks of herpes labialis (Burnet and Williams; 1939) but various workers have shown that no increase in antibody titre occurs in individuals with recurrent herpetic infections (Dudgeon; 1950, Holzel et al. 1953). Ross and Stevenson (1961) examined paired sera from fourteen herpetic individuals aged from two to seventy years who developed herpes labialis while in hospital with various pyrexial illnesses to ascertain if recurrent herpetic infection developing in the course of another infection might cause a rise in the level of herpes antibody in the serum. In no case was a fourfold or greater rise in complement fixation titre obtained.

At present it is generally agreed that the most reliable laboratory evidence of primary herpetic infection is the demonstration of a rising serum antibody titre during the illness and in the course of these studies a fourfold increase has been accepted as one of significant degree.

Primary /

Primary herpetic infection of the central nervous system with proof of the aetiological agent is rare but has been recorded both in infants and in adults (Smith et al.; 1941, Zarnfonetis et al.; 1944, Whitman et al.; 1946, Wildi; 1951, France and Wilmers; 1953, Greenfield; 1958 and van Bogaert; 1959). In these cases the diagnosis was established by the characteristic appearances of the central nervous system at necropsy, by the identification of intranuclear inclusion bodies typical of herpetic infection in the cells of the central nervous system on histological examination and by the isolation of the virus from cerebral tissue obtained at necropsy. Less frequently herpes simplex has been identified as the infective agent in the central nervous system of those who have survived herpetic meningo-encephalitis (Afzelius-Alm; 1951, Florman and Mindlin; 1952).

The serological tests employed to measure variations in the levels of herpes antibody are neutralisation tests in mice or in embryonated eggs, or complement fixation (C.F.) tests. Neutralisation tests are expensive in time and materials and there has been a general tendency, in recent years, to discard them in favour of C.F. tests. Dudgeon (1950), was among the first to employ a C.F. antigen prepared from the chorioallantoic membrane of the chick embryo (CAM) and this is now widely used in tests of this kind. Comparitive studies of neutralisation tests and complement fixation tests using CAM antigen were made by /

by Holzel et al.; (1953) and Sosa-Martinez and Lennett (1955) in primary and recurrent herpes infections and these authors found good correlation between the results obtained. Unsatisfactory results with CAM antigen have, however, been reported by some, (Afzelius-Alm; 1951).

In all cases in the present series where these investigations were carried out serological tests for herpes simplex were undertaken by the complement fixation technique using a CAM antigen. The antigen employed was obtained by a modification of the method of Sosa-Martinez and Lennette (1955). 0.25 ml. of a 10^{-2} dilution of CAM or yolk sac suspension of the HFEM strain of virus, containing approximately 1000 I.D. 50, was inoculated into the yolk sac of 7 - 8 day old embryonated eggs which were incubated at $36^{\circ}C$. Eggs dying before the 40th hour were discarded. Between the 40th and 50th hours, eggs were candled twice and those recently dead or sluggish were placed in a refrigerator and chilled from four to eighteen hours before harvesting. Chorioallantoic membranes and amniotic sacs were removed, rinsed with saline and drained. An equal volume of barbitone-buffered saline was added to the membrane which was then homogenised in a MSE masticator at maximum speed for three minutes and centrifuged at 2,000 r.p.m. for ten minutes. The supernatant fluid constituted the crude antigen which was modified as follows:-

(1) Non specific reactivity was removed by a fluorocarbon

compound /

compound (Gessler et al.; 1956). One part of the fluorocarbon "Arcton 113" (I.C.I. Ltd.) was added to two parts of the supernatant fluid prepared by the method given above and the mixture was homogenised for two minutes. It was then centrifuged at 2,000 r.p.m. for five minutes. The supernatant fluid was again treated with fluorocarbon, centrifuged as before and stored at 40°C.

(2) Optimal dilution of each batch of antigen was determined by chessboard titration against positive human serum. Human serum was used in place of type-specific sera prepared in guinea-pigs because preliminary experiments had shown that the optimal titre of the antigen against guinea-pig serum was higher than against human serum.

(3) Preliminary screen tests with a single dilution of 1 : 8 "convalescent" test sera were made against antigen at three dilutions, namely, optimal dilution as determined by chessboard titration, four times optimal dilution and one-fourth optimal dilution. This was necessary because it was found that the optimal dilution of the antigen varied with different human sera but not between paired sera from one individual. Titrations of each paired sera were then carried out with the dilution of antigen which showed optimal fixation.

Test sera were stored at -20°C before use. They were then thawed, diluted 1 : 8, and inactivated at 56°C for thirty minutes.

The /

The tests were carried out in plastic plates with 0.1 ml. volumes each of antigen dilution, serum dilution, and complement (four 50% haemolytic doses). Dilutions of all reagents were made in barbitone buffered saline. After standing at 4°C overnight, the plates were kept at 37°C for thirty minutes when 0.1 ml. 2% optimally sensitised sheep cells were added to each cup. The plates were left for a further forty minutes at 37°C, and were shaken at fifteen, thirty and forty minutes, and then allowed to settle at room temperature before reading.

In two instances in the present series (cases 9 and 10) serological investigations for a rise in antibody titre to herpes simplex, lymphocytic choriomeningitis mumps "S" and "V" and the adenovirus group were negative. In cases 13 - 18 inclusive which were traced as a result of serological findings, the magnitude of the C.F. antibody response to herpes bore no apparent relationship to the outcome of the disease.

Case No.	C.F. titre	Result
13	Rise X 8	Partial recovery.
14	Rise X 32	Rapid complete recovery.
15	Rise X 32	Death.
16	Rise X 8	Complete recovery.
17	Rise X 4	Partial recovery.
18	Fall X 16	Partial recovery.

The demonstration of a rising antibody titre for herpes is taken as evidence that encephalitis, in these cases, was the result /

result of the invasion of the central nervous system by this organism. The possibility that a dual infection might exist with an unknown virus affecting the central nervous system while the herpetic infection was confined to the mouth and upper respiratory mucosa, was discounted by the uniformly negative findings in complement fixation tests of titres for mumps, lymphocytic choriomeningitis, adenovirus, louping ill or influenza type A, B or C. All further examinations on faecal specimens by inoculation of amnion and/or monkey kidney tissue cultures and suckling mice were negative.

In only one case of the present series investigated was a virus isolated from specimens of brain obtained at necropsy. In this instance (case 7) the infective agent was recovered from a specimen of the mid brain and subsequent investigations showed that while it was present in this region in a concentration which apparently precluded contamination, it could not be isolated from other parts of the central nervous system. These findings are of particular aetiological interest and afford comparison with the results of the work of Levaditi and his colleagues upon similar cases in the third decade of this century. The purpose of the material set out in the following pages is to publish the evidence upon which the identity of the infective agent recovered in case 7 has been determined.

Specimens from the central nervous system in case 7 were removed at necropsy with sterile precautions and were placed in 50% glycerol saline. The bottles were stored at a temperature of 4°C. before despatch to Glasgow for virological examination.

Specimens /

Specimens obtained from the patient in case 7 at necropsy were investigated virologically with the following results:-

(a) Stool (415/58). This material gave negative results in monkey kidney tissue culture.

(b) Cerebral cortex (410/58). Negative results were obtained after inoculation of this material in HeLa cell culture and also after intracerebral inoculation of adult mice and intraperitoneal inoculation of suckling mice.

(c) Mid brain (414/58).

(i) Suckling mice were inoculated intraperitoneally with a suspension of this material and eight out of nine animals so treated died after an interval of four to five days. All the animals fatally affected showed spastic hind-limb paralysis exactly comparable with that seen in this species after intraperitoneal inoculation with a suspension of herpes simplex virus. The original suspension was titrated and this indicated the presence of at least 3000 I.D. 100 virus per gramme/brain. The upper limit of concentration was less than 300,000 I.D. 50 per gramme/brain.

(ii) The original suspension of material from the mid brain was inoculated intracerebrally into adult mice and two of four animals so treated died with spasm of the hind limbs.

Passage of mouse brain suspension from (c) (i) and (ii) /

(ii) gave rise to transmissible cytopathogenic effects in HeLa cultures. The same material killed chick embryos inoculated by the amniotic route and produced focal lesions on the chorioallantoic membrane of embryonated eggs. These lesions resembled those produced by herpes simplex virus in similar prepara-:tions. Eight mice inoculated intracerebrally all died with characteristic spasm of the hind limbs. A second passage suspension from these mouse brains was also lethal to mice on third passage. Second passage suspension inoculated on to the scarified cornea of rabbits gave rise to herpetiform keratitis and histological examination of these lesions showed the presence of typical herpetic intranuclear inclusions in cells of the cornea. Suspensions were made from the nictitating membrane from the infected rabbit's eye and this material was inoculated into the chorioallantoic membrane of embryonated eggs where it gave rise to focal lesions typical of those caused by herpes simplex. The suspension of nictitating membrane was passed serially eleven times by the chorioallantoic route and then submitted to neutralisation tests on chorioallantoic membranes by the "pock-counting method". The agent was not neutralised by louping-ill sheep antiserum, normal sheep, or by normal guinea pig /

pig serum. Significant neutralisation was however observed with herpes antiserum derived from a guinea pig supplied by courtesy of Sir Samuel Bedson.

(iii) Intracerebral inoculation of a rabbit was followed by death on the eleventh day. Histological examination of half of this brain showed severe perivenous cuffing (case 7, Fig. 14) but intracellular inclusions were not observed either in nerve or in glial cells.

(iv) A guinea pig survived an intracerebral inoculation and was hyper-immunised by intraperitoneal injection of HeLa tissue-cultured virus. The animal was killed and bled out. Serum from this animal was utilised in (v).

(v) The transmissible cytopathogenic agent in HeLa tissue cultures was isolated in titre equivalent approximately to 5000 I.D. per gramme/brain. This agent was carried in eight serial passages and gave rise to clumping, rounding, proliferation and nuclear ballooning of cells. These changes were typical of those produced by herpes simplex virus. Neutralisation tests were carried out in tissue culture and the agent was neutralised by herpes antiserum (Bedson's guinea pig antiserum) and by the serum of the guinea pig immunised with homologous agent ((iv) above) in a dilution of 1/16. Neutralisation was not effected by normal guinea pig serum or by serum from case 6.

The virus isolated from the mid brain has been identified as herpes simplex virus in virtue of its typical host range, pathogenicity, type of lesions produced on chorioallantoic membranes, cytopathogenic effect on HeLa tissue culture, characteristic keratitis produced in the rabbit cornea, typical nuclear changes and intranuclear inclusions in the cells of the rabbit cornea and in HeLa cell cultures, and by specific neutralisation with standard herpes antiserum.

The validity of the foregoing results is established in view of the following considerations. Specimens of cortex and mid brain were processed and inoculated at the same time by a non-herpetic individual (N.R.G.) in a laboratory where herpetic material had not been handled during the preceding twelve months. Despite the utilisation of the same fluids for extraction, the suspension of cortical material ((b) 410/58) gave negative results while the mid brain suspension ((c) 414/58) was positive. The mid brain extract gave positive and typical reactions in several different host systems inoculated on more than one occasion and the observations made were therefore capable of repetition. Intracerebral pathogenicity of unadapted strains of herpes simplex for adult mice is not high and the deaths of two out of four adult mice inoculated intracerebrally after an incubation period of only four days indicates the presence of virus in appreciably high concentration. This finding is supported /

supported by the titrations in tissue culture and in suckling mice and these indicated the presence of virus of the order of 5000 I.D. 50 per gramme of brain tissue. A concentration of this magnitude is higher than could conceivably be expected as a chance finding of contamination of the specimen. It has not proved possible to trace any published records of systematic titrations carried out on brain tissues of alleged chronic herpes carriers, and figures are not, therefore, available for comparison. It is considered unlikely, however, that the virus is present in such cases in comparable concentration to that found in the mid brain of this case. Large intranuclear eosinophil inclusion bodies were seen in histological preparations from the cornea of the inoculated rabbit's eye and the affected nuclei showed also margination of the nuclear chromatin. This tissue, however, is well known to be highly favourable for the demonstration of these changes. The fact that similar inclusion bodies were not found in material from the rabbit's brain (c;iii) or in material from suckling mice (c;i) was not unexpected in view of previous experience of the difficulty or impossibility of finding such inclusions in the tissues, other than the cornea, of experimental animals infected with known strains of herpes simplex.

The strain of herpes simplex virus isolated from the mid brain of the patient in case 7 has been designated 414/58. All investigations to date have failed to reveal any neurotropic agent other than herpes simplex in this material.

The /

CHAPTER IV

DISCUSSION

The neuropathological classification of the encephalitides is based upon macroscopic and morbid histological findings. Greenfield (1958), in discussion of the histological diagnosis of encephalitis lists cellular infiltration, microglial hyperplasia, nerve cell changes, inclusion bodies, lesions of the white matter and vascular changes as types of reaction found in all forms of encephalitis. It is generally recognised however, that the reactions of the brain in inflammation are somewhat stereotyped although they vary both in emphasis and distribution. In the absence of any organism of known identity the pathological diagnosis in any single case is empirical and is descriptive of the predominant lesion.

In the present work, eighteen cases believed to be examples of inflammatory changes in the central nervous system and occurring in association with epidemic influenza are described. The neuropathological diagnosis in cases 1 (ii), 5, 7, 8 and 15 rests upon necropsy and morbid histological findings as detailed in the Appendix. The identification of the herpes simplex virus recovered from the mid brain in a single case (case 7) is discussed in chapter III. In case 7, however, the pathological changes in the central nervous system were not typically those of acute herpetic encephalitis. On the other hand, case 15 displayed pathological changes typical of acute herpetic encephalitis with a significant rise in herpes antibody titre, but inclusion bodies were not seen in any cells and /

and all attempts to isolate a virus were unsuccessful. In cases 2, 3, 4, 6, 9, 11 and 12 the diagnosis is based upon clinical findings and the natural history of the disease. In case 10, the putative diagnosis is based upon the isolation of Coxsackie virus from the stool. In cases 13, 14, 16, 17 and 18 the diagnosis of herpes simplex meningo-encephalitis or myelitis rests upon clinical and serological evidence.

The prodromal upper respiratory infection which occurred in cases 1 (ii), 3, 4, 6, 7, 8, 11, 12, 13, 14, 15, 16, 17 and 18 was confirmed virologically as influenza in one instance (case 8) where influenza virus type A was isolated from lung at necropsy. In other cases where there is clinical or epidemiological evidence to suggest that the prodromal respiratory infection was influenzal in nature details are given in the Appendix.

The first three cases of the series presented (case 1 (first admission), case 2 and case 3) together are regarded as examples of the same illness forming a small group of obscure aetiology. Cases 2 and 3 are regarded as abortive forms of the illness. There is evidence that similar illnesses were not infrequent when the influenza epidemic was at its height in Renfrewshire early in October 1957, but because of the stress of prevailing conditions and because of the rapid recovery of patients, records are inadequate and the material cannot be properly documented. It is open to question whether these three cases share a common aetiology and proof of common origin cannot be obtained from the evidence available. On the other hand, /

hand, all three presented at hospital within a period of six weeks and all showed closely similar clinical features. In these circumstances it is regarded as unlikely that two or more different causes were responsible for these illnesses. Although the current epidemic of influenza was not generally recognised in Renfrewshire until the middle of September 1957, sporadic cases were present in the area a few weeks before this date. When the epidemic was at its height in late September and early October 1957 it is known that a number of cases closely resembling case 1 (first admission), case 2 and case 3 was observed. In view of these circumstances, therefore, these three cases are regarded as mild and abortive forms of meningo-encephalitis related to the epidemic of influenza. The second and fatal illness in case 1 (26.1.58) certainly followed hard upon an acute respiratory infection. The morbid histological features in the central nervous system in case 1 (second admission) were strongly suggestive of a violent anaphylactic reaction and these features taken in conjunction with the time interval of five months between the first and second admission of case 1 go some way to suggest that the central nervous system of this patient had been sensitized in August 1957 and that a second exposure to the same antigen in January 1958 precipitated a fatal allergic encephalitis.

On clinical grounds, cases 4, 11 and 12 are considered to be mild forms of encephalitis presenting primarily as psychotic disturbances /

disturbances and several accounts of cases bearing many features in common with those in cases 4, 11 and 12 presently reported have been published in recent years. Lisitsa (1950) described three cases of a form of encephalitis with psychotic manifestations occurring in Tadjikistan in the spring of 1948. Bickerstaff and Cloake (1951) reported three cases occurring within eighteen months in which the clinical findings were so similar as to justify their inclusion in a single group. In each case there was a rapidly developing disorder of the brain stem associated with mental derangement. Parkinsonism appeared as a short episode in one case. The authors preferred to name these conditions mesencephalitis and rhombencephalitis in view of their findings. All patients recovered, but the cause or causes remained unknown although a virus infection or demyelinating disorder of the type of acute disseminated sclerosis were considered as possible diagnoses. Similar disturbances of behaviour in children with measles encephalitis were recorded by Meyer and Byers (1952) and these authors showed that in one case in three, recovery was excellent. Brewis (1954) attempted a classification of ninety three cases of encephalitis in Durham children on the basis of symptoms and clinical observations. The short-term sequelae of Western Equine and St. Louis encephalitis were reported by Finley et al. (1955) and these authors noted mental retardation, abnormal behaviour and mild emotional disturbances in some instances. Psychotic manifestations were not a feature of the sequelae in Rubella encephalitis in Danish children reported by Schleisner

et /

et al. (1955) but a smaller series of cases of the same disease reported from Copenhagen by Jorgensen (1955), including some adults, showed coma, delirium and periods of motor excitement. A very interesting report of twenty six cases of an unusual type of encephalomyelitis occurring at Vilyui was given by Shapoval and Sarmanova (1955). This particular disease was localised in a restricted area of Russia where a disease with similar features had been recognised for many years. The onset was acute and febrile and this was often followed by clouding of consciousness with somnolence and diplopia; monotonous speech and emotional lability were also recorded. In some cases the sequelae after several years included facial, glossopharyngeal, vagal and hypoglossal nerve palsies. Espir and Spalding (1956) describing three cases of encephalitis occurring in British patients in the United Kingdom (one case) and in Germany (two cases) were prepared to entitle these as cases of encephalitis lethargica on clinical grounds. The features described resemble those of case 4 of the present series, but are more severe. An interesting finding was that of marked character deterioration in a male patient of sixteen years resulting in the commission of a series of crimes. Both the other patients in this report were also male. Radermecker et al. (1957) reporting from Antwerp gave an account of meningo-encephalitis of undetermined origin with a strong psychotic component and favourable outcome. All four patients were /

were young adult males and the numerous symptoms included those of hallucinations, childishness and psychopathic reactions; pain in the upper abdomen and vomiting were also recorded. The disease was benign and resolved within four months.

The pandemic of influenza in 1957 was attended by a number of psychotic and neurological disorders similar to those in cases 4, 11 and 12 of the present report. Bental (1958) describes three cases of children showing anxiety, confusion and restlessness as the most important symptoms. These were benign conditions resolving within three weeks and showing relapse in only one instance. An account of psychosis following Asian influenza in Barbados was given by Still (1958), and similar cases are reported by Kapila et al. (1958) in South India. The patients in the Barbados series of average age of twenty eight years included fourteen females and five males. Hallucinations were prominent in the symptomatology which also included restlessness and aggressive behaviour. The disease, often treated by electroconvulsive therapy, was benign and patients were discharged from hospital after an average stay of thirty eight days. McConkey and Daws (1958) also described four patients with severe neurological disorders following a short febrile illness and they regarded three of their four cases as instances of encephalitis.

Cases 13, 14 and 16 are regarded as examples of herpetic meningitis or meningo-encephalitis with varying degrees of recovery /

recovery while case 15 is an acute and fatal form of the same disease. Case 18 is believed to be an example of chronic herpetic myelitis and the slow evolution of the disease affords a comparison with the clinical features of case 6. Case 17 is regarded as chronic herpetic encephalitis presenting, in this instance, with profound disorder of the sensorium. Similar clinical features are present in case 7. This latter case is the only fatal one in the present series on which virological studies were made at necropsy with positive results.

The strain of herpes simplex virus (414/58) isolated from mid brain suspensions in case 7 is regarded as authentic and all virological investigations so far made, support this conclusion. On the other hand, the lesions in the brain of case 7 do not resemble those described by many authorities as typical of herpes simplex encephalitis (Smith et al.; 1941, Zarafonetis et al.; 1944, Whitman et al.; 1946, Wildi; 1951, France and Wilmers; 1953). The cases of France and Wilmers and that of Wildi referred to newly born infants who succumbed to the infection within sixteen days of birth; that of Smith et al, also an infant, succumbed within five weeks of birth. It may be that these cases do not afford appropriate standards of histopathological comparison with case 7 presently reported, where the patient was thirty three years of age, in view of the differences in myelination due to differences in age. However, the case described by Zarafonetis et al. was that of fatal herpes simplex encephalitis in a male aged twenty five years /

years and the two fatal cases described by Whitman et al. referred to males aged twenty six and twenty eight years; these are all comparable with case 7. In these cases, whether infants or adults, there is a close similarity in the morbid anatomical and histological findings. Thus, Smith et al. report a brain 'unusually soft even for a young infant', and these authors also reported large areas of necrosis in the cerebral hemispheres with many fat-laden phagocytes. The cerebral vessels in these cases were well preserved. Intranuclear inclusion bodies typical of herpes simplex, with a clear zone about the acidophil inclusion and margination of nuclear chromatin were numerous. The virus was readily transmitted to mice and rabbits where it gave rise to typical herpetic lesions. Zarafonetis et al. in their case of a man aged twenty five years reported an area of softening four centimetres in diameter along the inferior margin of the right temporal lobe. Again, typical intranuclear inclusions were reported in profusion and hamsters were inoculated with material from the brain with typical results. The first case of Whitman et al. was that of a man aged twenty six years and the brain was described as "soft and mushy"; the cortex of the right parieto-occipital region displayed severe malacia with very numerous gitter cells showing vacuolated cytoplasm. Typical intranuclear inclusion bodies were found in subcortical astrocytes. The second case, that of a man aged twenty eight years, showed areas of softening in the right temporal and occipital lobes of the cerebrum with profuse phagocytic infiltration /

infiltration. Inclusion bodies were found in the astrocytes of the cortex. The two viruses obtained from these cases were passaged serially in mice, guinea pigs, rabbits, hamsters and the chorioallantois of chicks. Inclusion bodies again were demonstrated in material from all these experimental animals. In the case reported by Wildi, intense changes were found in the uncal and hippocampal regions of both sides and these were visible macroscopically. Eosinophil intranuclear inclusions in the ganglion cells were extremely numerous in the rhinencephalon. The diagnosis of herpes simplex encephalitis was confirmed by animal inoculation and culture of the virus. In the cases of France and Wilmers, the brain in the first case was "too diffluent to allow of detailed examination" but in the second case the brain was externally normal and contained numerous round white nodules of firm consistency resembling those found in the liver in the first case described by these authors. Typical eosinophil inclusions were present in liver cells but not in the brain of the first case, while in the second case, inclusion bodies were not found either in the liver or in the brain and this affords comparison with the findings in case 15 of the present series. Animal inoculation and virological studies were not recorded in this report. The close correspondence in the accounts of these authors leaves little room for doubt that the virus of herpes simplex can give rise to a fatal form of encephalitis with the characteristic /

characteristic features described and these are also illustrated in case 15 of the present series. It is also clear, however, that this form of encephalitis differs markedly from that found in case 7 of the present series. It is therefore convenient to refer to the disease described by Smith et al.; (1941), Zarafonetis et al.; (1944), Whitman et al.; (1946), Wildi; (1951), France and Wilmers; (1953) and case 15, as acute herpetic encephalitis.

The identity of the virus isolated in some of the foregoing cases is not in dispute and it is accepted as herpes simplex while the ease with which the agent has been isolated and the presence of typical intranuclear inclusions in the morbid histology of these cases, make it almost certain that the encephalitis is the result of a widespread infection by herpes simplex. This aetiological link between the herpes virus and some forms of acute encephalitis has been accepted by the majority of authors on this subject.

The presence of herpes simplex in the body fluids of some healthy subjects was established at an early date after attention had been drawn to the results of virological investigation in cases of encephalitis lethargica (Levaditi, Harvier and Nicolau; 1921 (a)). Since this date the virus has often been demonstrated in the body fluids both of normal persons and of those suffering from other diseases (Greenfield; 1958) and these findings have supported a widespread opinion that /

that the organism may exist symbiotically with its host in some cases and might be isolated in some cases of encephalitis as a matter of chance, although studies to determine the concentration of the virus in these carrier individuals have not been traced. It was further pointed out, that, on purely epidemiological grounds, the infectious aetiology of encephalitis lethargica was very suspect since cases tended to occur individually. Thus, Smith (1921), in an American epidemiological study, reported a series of nine hundred contacts with a case of encephalitis lethargica without a single reappearance of the disease, and in France, Bernard and Renault (1920) showed that there was no evidence of direct contagion in four hundred cases. Suspicion fell naturally upon sub-acute cases as a reservoir of infection but investigations disclosed that these could not account for the majority of the instances in which encephalitis lethargica declared itself. On the other hand epidemics of the disease were described and McNalty in the Ministry of Health Report (1922) and Zinsser (1928) both described such outbreaks within closed institutions.

It is necessary, therefore, in the first place, to establish the validity of the identification of the virus isolated in cases of encephalitis lethargica as herpes simplex. The first report of such an isolation was given by Levaditi and Harvier in 1920 (a) and since this date other strains of the same virus in a total of some twenty cases, have been isolated in /

in similar circumstances. Levaditi isolated three strains which he identified as herpes simplex, but strain C on which most work subsequently was carried out was obtained from a patient with encephalitis lethargica who was suffering at the same time from facial herpes. As it is well known that the virus may be found in the cerebrospinal fluid of patients with herpetic lesions, the validity of this isolation is open to question (van Rooyen and Rhodes; 1948). The second strain (CH) was isolated by Levaditi et al. (1922) from the naso-:pharynx in a case of encephalitis, but again this strain is suspect because the nasopharynx is known to harbour the virus in some normal persons. The third strain isolated by Levaditi and Harvier was from the brain of a choreiform case of encephalitis and this agent was passaged by intracerebral inoculation in rabbits. This strain, whose validity seems unexceptionable was of low virulence and was not maintained. After this date, various workers succeeded in isolating herpes simplex from the brains of cases of encephalitis lethargica, but, in all, only some twenty successful isolations have been recorded. Numerous investigations carried out by other workers in this field entirely failed to isolate a virus from cases of this disease and various explanations were advanced to account for this lack of success. Levaditi and Nicolau (1924) elaborated the theory of autosterilisable neuro-infections while other workers in the same school drew attention to the action of glycerol in "unmasking" the virus by destroying a factor /

factor present in brain which exerts an inhibitory effect on the infective agent. As some of those who had failed to isolate a virus from cases of encephalitis lethargica had used fresh human brain or cerebrospinal fluid this observation may be of significance. In case 7 of the present series the specimens from the central nervous system were stored in 50% glycerol at 4° Centigrade for forty eight hours before transmission to the virological laboratory. Perdrau (1925) was unable to isolate any virus from the fresh brain of a case of encephalitis lethargica and this material proved avirulent on injection into experimental animals. When brain tissue from a rabbit immune to herpes was added to the suspension of human brain, a herpes virus was successfully isolated from the mixture. Perdrau was of the opinion that the herpes virus, latent in the brain from the case of encephalitis lethargica was stimulated by an "aggressin" present in the additive.

The identity of the agent isolated in cases of encephalitis lethargica has frequently been in question, but, at present, a large measure of general agreement exists that the virus is identical with herpes simplex. What is at issue is whether the herpes simplex virus is the cause of encephalitis lethargica. Levaditi writing in 1922, stated, "Le virus d'herpès et celui de l'encéphalite épidemique "sont de même nature. Le premier n'est qu'une variété moins "virulente du second" (Levaditi et al.; 1922). This author was /

was also of the opinion that many normal persons harbour strains of herpes simplex in the saliva. Levaditi distinguished between these strains in terms of the lesions they could produce on inoculation into the conjunctival sac of the rabbit. In this way he came to the conclusion that eighty per cent of normal persons harbours a keratogenic strain, and fifteen per cent an encephalitogenic strain, within the saliva, both strains being typical of herpes simplex and he was of the opinion that the virus exists in the saliva in an attenuated form between epidemics of encephalitis. (Levaditi, Harvier and Nicolau; 1921). When an epidemic occurs, whether because of lowered resistance of the host, or an increase of virulence in the virus, or both, dissemination of the infection takes place and encephalitis results. Although it is known that the virus can be isolated on occasion from saliva, Levaditi's high estimate of the proportion of carriers of herpes simplex in the population is not generally accepted, and his theory of the aetiology of encephalitis lethargica is unsupported by experimental work in man. Many reports of viruses other than herpes simplex, isolated from human cases of encephalitis lethargica, have been invalidated because of failure to recognise the presence of encephalitis cuniculi in experimental rabbits or because of inadequate control experiments or bacterial contamination.

There is a possibility that other infective agents may exist /

exist whose features so closely resemble those of herpes simplex that they may be confused with this agent. Such are the "B" and "W" strains of virus isolated from a fatal human case of ascending myelitis occurring in a laboratory worker after a bite on the hand from a monkey. (Gay and Holden; 1933, Sabin and Wright; 1934). Some workers have since regarded the "B" and "W" strains isolated as identical; while Sabin (1934) thought that the "B" strain closely resembled herpes simplex, Haber (1935) identified the "B" strain as the virus of herpes simplex but these findings are not now generally accepted. It is clear that the ultimate solution of such problems must await improvements in virological technique and while recognition is given to this source of confusion, present identification of viruses can be made only within current terms of reference.

The route taken by herpes simplex in reaching the central nervous system has been the subject of much experimental work and the possibility that transmission may take place by way of the blood stream has often been studied. Doerr and Vochting (1920) who first reported encephalitis following corneal inoculation of this agent in rabbits, also were able to demonstrate the same result after intravenous injection. Levaditi (1926), after reviewing the subject, was of the opinion that there is a transitory appearance of the virus in the blood stream during the acute phase of infection although proliferation does not take place in the blood. The work of Goodpasture /

Goodpasture and Teague (1923-4) on this subject, in America, was matched by that of Marinesco and Draganesco (1923) in Rumania about the same time. In both these investigations a neurotropic strain of herpes simplex was used and its centripetal migration to the brain was demonstrated from the sites of inoculation, first in the cornea, and later in the masseter muscle of the rabbit. After corneal inoculation, both teams showed, from the traces of damage left in its wake, that the virus had traversed the sensory nerves of the eye to the Gasserian ganglion whose cells it injured, and thence had passed to the brain stem at a level corresponding to the central connections of the fifth nerve. These observations were confirmed by those of Friedenwald (1923) who showed that in rabbits with experimental herpes keratitis, the virus could be recovered from the Gasserian ganglion. In similar fashion, Flexner and Amoss (1925) showed that herpes simplex introduced into the scarified abdominal skin of a rabbit at first produced a local reaction typical of the virus. This was later followed by an ascending myelitis in corresponding segments of the spinal cord and the process terminated in a fatal encephalitis. Goodpasture and Teague also showed that the virus followed branches of the vagus nerve after injection into the tracheal mucosa and branches of the motor division of the mandibular nerve after injection into the masseter muscle of the rabbit. Similarly, intrahepatic injection of the virus was followed by its transmission along sympathetic filaments. In all cases, the /

the first parts of the brain to be affected were those corresponding to the central connections of the nerves involved. Goodpasture (1925) demonstrated also that in rabbits brought into contact with infected animals the portal of entry was the mucosa of the mouth, nose or throat, and lesions first appeared in the central nervous system by way of the sensory distribution of the fifth and ninth nerves. It is also noteworthy that inclusion bodies typical of herpetic infection were not seen in the morbid histology of these experimental animals. While Goodpasture was of the opinion that the infective agent in these experiments was propagated along the axons, other workers, after further experimental studies, held the view that the route of spread was by way of tissue spaces and vessel sheaths of nerves. The work of Field (1952), on the whole, tended to support "lymphatic space" progression rather than axonal transmission, but, as this author pointed out, differences may result, in some measure at least, from the use of different strains of virus. It is also possible that the suggested methods of spread are not mutually exclusive (cf. Black and Melnick; 1955), although the nature of the mechanism involved in either case is at present obscure. Field illustrated inclusion bodies within glial nuclei in the affected portions of the medulla but he did not report these structures within nerve cells. Black and Melnick (1955) discussing the microepidemiology of poliomyelitis and herpes - B infections showed experimentally that, in the absence of immune serum, herpes - B virus is able to spread from cell to cell /

cell by two different routes. The first is by "cell-bridges" from infected to neighbouring cells and the second, after a latent period of sixteen to twenty hours, is by passage through the culture medium to cause new foci of infection some distance from the original host cells. Addition of immune serum to the system blocks this latter mode of dissemination.

These findings offer considerations of interest in comparing the neuropathological lesions in cases 7 and 15 of the present series. In case 7, herpes simplex virus was isolated from specimens of mid brain in a significant concentration which excluded the possibility of accidental contamination. At the same time and under the same conditions, the virus was not isolated from specimens submitted from the cerebrum. It was further apparent in the morbid histology of this case that within the pons severe perivenous cuffing, vascular necrosis and foci of microglial proliferation were present. It should be borne in mind that the portion of mid brain selected for virological examination was selected for the reason that the macroscopic appearances suggested the presence of very numerous lesions. This material was not then available for morbid histology. It is reasonable to conclude that the site from which the virus was isolated was also the site of maximum density of neuropathological lesions. It may be deduced from these findings that herpes simplex was the aetiological agent in this case and that the virus was concentrated about the mid brain. The severe lesions encountered in the corpus callosum and corona radiata showed /

showed a higher proportion of haemorrhagic forms and both ball and ring haemorrhages are known to be early responses of the brain in many forms of encephalitis. Recent experimental work has tended to suggest that the presence of a virus in the central nervous system may give rise terminally to a generalised vascular response which some authors regard as allergic in pathogenesis (Terai; 1955) and these findings may be of significance in this connection. The general neuropathological findings, however, in this case with a measure of localisation of the lesions differ markedly from those widely accepted as typical of herpes simplex encephalitis as previously discussed.

On the other hand, the neuropathological appearances in case 15 compare closely both macroscopically and in morbid histology with those generally accepted as typical of acute herpetic encephalitis. There are two important exceptions; inclusion bodies were not found in any section examined and virological examination of specimens taken under optimum conditions failed to isolate any infective agent. This failure was more striking since the investigations were undertaken in the expectation of a positive result as the herpes simplex antibody titre had shown a thirty-two fold rise in the course of the illness.

These observations do not afford more than an indication of possible lines of thought in consideration of the pathogenesis of this group of diseases. The series of cases on which this work is based is too small to afford acceptible proof /

proof of any hypothesis and in many respects, for reasons already discussed, the investigations and findings in the cases themselves are incomplete. With the proviso that proof lies outside the scope of the present work it may still be of value to consider some rationalisation of the phenomena observed.

In the past there has been considerable support for some relationship between encephalitis lethargica and influenza. Von Economo (1931) admits there is good historical evidence for this. He writes, "It would be equally futile to deny any epidemiological connection between influenza and encephalitis lethargica", and concedes that epidemics of sleepy sickness e.g. Nona and Sydenham's epidemic seem to have occurred after or before many of the great influenza epidemics.

He states "Epidemiologically.....a certain relationship with influenza may be asserted with a degree of probability bordering on certainty and this relationship seems at times to exercise a directing influence on the disease, as is demonstrated by the severe degree of toxicity of the hyperkinetic cases during influenza epidemics. What this epidemiological relationship consists in, whether in identity of virus, in its biological variability, in a complex group community, in a casual symbiotic coupling, or in a connection of different, as yet unknown order, must be left for the present an open question until further research is rendered possible by future epidemics".

There is evidence that herpes simplex may gain the neuraxis by neural transmission in experimental animals (pp. 95 - 97). If a similar process were operative in man it could offer an explanation /

explanation of the relative localisation of lesions as seen in case 7 and the fact that the virus was isolated only from the mid brain. In contrast, the incidence of massive encephalomalacia in case 15, suggests a haematogenous route in the dissemination of the virus.

Studies in immunology with reference to herpes simplex infection of the central nervous system have given rise to many confusing results. Doerr and Schnabel (1921) showed that herpes-immune rabbits resisted corneal and intracranial injection of encephalitic strains of the virus and they found also that animals recovering from a corneal infection with encephalitogenic strains were locally and generally immune to the virus. If, however, it is conceded that the virus may gain the neuraxis by propagation along nerve filaments, it is evident that small infecting doses of the organism may give rise to focal lesions in the brain stem. Moreover, if propagation within the brain were electively by cell-bridges, the condition of viraemia would not arise in the first instance, and antibodies might not be formed in sufficiently high titre to be detectable. Some experimental evidence is available to support this suggestion. The work of Wildy (1955) on the spread of herpes in the nervous system of mice showed that when the agent was introduced atraumatically by multiple pressure technique into the paw of the hind foot almost all the animals developed myelitis. It was possible on two grounds to exclude the possibility /

possibility that a viraemia occurred during transmission. In the first place the syndrome rarely followed an intravenous injection of the virus unless the central nervous system had previously been traumatised and secondly by observing that the intravenous injection of anti-herpes serum neither delayed the onset of paralysis nor prevented the virus gaining access to the central nervous system.

It is generally agreed that the herpes simplex virus can exist symbiotically in the nasopharynx or in the salivary glands of a substantial proportion of the population in any community. Some of the determining factors in the transformation of a commensal virus into an active pathogen may lie in alterations in the natural barriers at the sites of inoculation and transmission but it is difficult to assume that the link between encephalitis and influenza is one of simple irritation or inflammatory change in the respiratory mucosa since similar alterations occur in the respiratory mucosa in many conditions not associated epidemically with encephalitis. It seems likely that other factors, at present unknown, are of importance. Cases of acute leucoencephalitis of undetermined aetiology occur sporadically and the clinical history in many instances records the symptoms of an upper respiratory infection appearing a few hours or days before the onset of neurological signs. This syndrome has been generally accepted as prodromal in many cases of /

of acute encephalitis and a possible aetiological role has not been assigned to it. Virological studies, however, on specimens obtained at necropsy from different regions of the central nervous system have been seldom recorded in these reports. It is generally accepted that peripheral injuries to nerves give rise to alterations in the permeability of the blood-brain barrier at their central connections and the increased incidence of poliomyelitis after tonsillectomy and inoculations is possibly attributable to changes of this kind. It may be that certain infections of the respiratory mucosa similarly cause changes in the central connections of the relevant nerves giving opportunity for a commensal to establish itself as a pathogen within the nervous tissue of the host. The concept of synergistic action between invading organism has been long accepted in bacteriology and in recent years attention has been drawn to the phenomena of interference between viruses (Jordan and Duffy; 1952, Duffy et al.; 1952).

In view of the foregoing considerations infection of the central nervous system by the herpes simplex virus may be tentatively classified in two main forms. In the first, acute herpetic encephalitis, the main weight of attack falls upon the neural cortex and its immediate integument. The area affected is very extensive and, in fatal cases, the damage is severe both in the cortex and in the leptomeninges. This form of /

of the disease tends to run a shorter and more acute course - either with recovery or death - than the other. The extent of damage and the extent of the area affected suggest a possible haemal route of infection with topographical spread through the medium of the cerebrospinal fluid as well as by direct extension from infected areas. In these cases also it is possible that the initial mass of infecting agent is large or that in such individuals conditions are particularly favourable to rapid multiplication of the virus. In the second form of the disease the attack falls initially upon the neuraxis and these cases tend to run a more chronic clinical course. Here, it may be that the initial infecting dose of the virus is small and its subsequent spread to higher or lower levels is largely from one group of nerve cells to another by transmission along inter-connecting nervous filaments. The localisation of the disease process suggests a neural route of infection. Terminally, in either form, the presence of the virus may precipitate a generalised allergic response within the central nervous system. The lesions may then include multiple foci of demyelination and peri-vascular cuffing, but, more commonly, the findings are those of widespread vasculitis giving rise to multiple /

multiple petechial haemorrhages and to the characteristic appearances in the brain as seen at necropsy.

CHAPTER V

CONCLUSIONS

The following conclusions have been reached as a result of the foregoing studies in encephalitis.

1. Epidemics of influenza in earlier centuries were often accompanied by outbreaks of encephalitis frequently presenting with the characteristic symptoms of lethargy or catatonia.
2. The epidemic of encephalitis lethargica which occurred at the time of the influenza pandemic of 1918 was almost certainly a recurrence of a phenomenon previously observed and not the first appearance of a new association of diseases.
3. The influenza pandemic of 1957-58 was accompanied by an outbreak of meningo-encephalitis generally of mild form and much less severe than the outbreak of 1918-19. The eighteen cases in the present report include six fatal cases. Transient Parkinsonism was noted in one case, but, so far, no typical examples of post-encephalitic Parkinsonism have occurred in twelve surviving patients. It is suspected, but cannot be proved, that some of the cases were similar to those of von Economo's encephalitis.
4. In the outbreak of encephalitis lethargica in the epidemic of 1918-19 the virus of herpes simplex was first implicated in the aetiology of the disease.
5. The same virus has been isolated in significant concentration from the mid brain of one case of encephalitis in the series presently reported, but, in this case, the morbid histologi-:cal findings were those of acute perivenous meningo-encephalitis and were not those of acute herpetic encephalitis. /

encephalitis. Serological evidence indicates the implication of herpes simplex as the aetiological agent in some other cases with symptoms referable to the central nervous system.

6. A tentative classification of herpetic infection of the central nervous system is proposed in two main forms:-
(a) Acute herpetic meningo-encephalitis with widespread involvement of the cerebrum and its integument
(b) Focal lesions of the neuraxis with little or no involvement of the hemispheres.

7. The association of epidemic influenza and encephalitis might suggest that the respiratory infection may promote invasion by some other agent, possibly herpes simplex, and may act synergistically in the transformation of such an agent into a pathogen.

8. A diagnosis of any variety of encephalitis is open to question in the absence of comprehensive virological investigation both in life and at necropsy.

9. The present investigation has not revealed whether the eighteen cases described were due to one aetiological agent common to all or whether there were several different causes.

10. Serological investigation and virological studies would seem to implicate the virus of herpes simplex in seven cases of the present report but the pathological findings in five of the eighteen cases coming to necropsy showed the features of acute perivenous encephalitis in two cases and those of acute allergic encephalitis in the remaining three cases.

CHAPTER VI

SUMMARY

Evidence of the historical association between epidemics of influenza and outbreaks of encephalitis is reviewed with reference to previous records.

The clinical and pathological material of the present study include seven cases of encephalitis associated with the influenza epidemic of 1957-58 in Renfrewshire presented with clinical and pathological reports. Of these, two were regarded as mild examples of allergic encephalitis with recovery, while the third case, readmitted to hospital after an interval of five months, succumbed to acute meningo-encephalitis after a second short illness. The fourth case reported was a mild illness with psychotic features which ended in recovery. The fifth was acute and fatal. The remaining cases included one of a short and fatal illness, acute perivenous encephalitis, and a chronic fatal encephalitis clinically resembling the sub-acute form of the disease described by van Bogaert. Three further cases are presented and these occurred in the same area but were unassociated with the influenza epidemic of 1957-58. A second group of eight cases with clinical and serological features for comparison is included from clinical and laboratory records made available in Glasgow.

The material presented is reviewed from the aspects of epidemiology and social medicine and the aetiology and diagnosis of each case is discussed separately.

Earlier /

Earlier work on the finding of herpes simplex in cases of encephalitis lethargica in the epidemic of 1918-20 is reviewed and is correlated with more recent experimental studies on the behaviour of this virus. The evidence thus assembled is related to the material currently presented. The association between epidemic influenza and outbreaks of encephalitis lethargica is considered to indicate the possibility that the respiratory infection promotes the transformation of a commensal virus into a pathogen perhaps by injury at the site of entry and possibly by synergistic action between the two viruses.

CHAPTER VII

ACKNOWLEDGMENTS

The assistance of all those who have helped by criticism and advice in the preparation of this work is acknowledged with thanks.

The kindness of the clinical staffs in the following hospitals in granting access to patients and clinical records is gratefully acknowledged; Gateside Hospital, Greenock; Larkfield Hospital, Greenock; Stobhill Hospital, Glasgow; Royal Mental Hospital, Glasgow; Ruchill Hospital, Glasgow; Crichton Royal Hospital, Dumfries; Law Hospital, Carluke. Virological and serological studies were undertaken by the Department of Virology, University of Glasgow. Photographs of pathological preparations were taken in the Pathology Department, Western Infirmary, Glasgow, with the help of Mr. G. Kerr.

The work of Miss Beatrice McCallum is acknowledged with gratitude in the preparation of the typescript.

CHAPTER VIII

REFERENCES

ADAMS, R.D., CAMMERMYER, I., and DENNY-BROWN, D. (1949),
Acute necrotizing haemorrhagic encephalopathy.
J. Neuropath. 8, 1.

AFZELIUS-ALM, L. (1951).
Aseptic (non bacterial) encephalo-meningitis in Gothenburg 1932-1950, clinical and experimental investigation with special reference to virus of herpes, influenza, mumps and lymphocytic choriomeningitis.
Acta. med. Scand. 263, 1.

ALDRIDGE, H.E. (1956).
Acute haemorrhagic leucoencephalitis.
Brit. Med. J. II, 807.

ALPERS, B.J. (1928).
So-called 'brain purpura' or haemorrhagic encephalitis; clinicopathologic study.
Arch. Neurol. Psychiat., 20, 497.

ALVARD, E.C., CONNELL, J.W., LUDD, A.T., and KELLNER, A. (1948).
The effect of pyribenzamine in beeswax on experimental meningo-encephalomyelitis in the guinea pig.
J. Immunol. 60, 345.

APPEL, K.E., BOND, E.D., and MORRIS, H.H. (1956).
Relationships between child and adult psychiatry. Results of treatment in post-encephalitis behaviour disorders, as shown in a follow-up study after twenty-five years.
Univ. Michigan Med. Bull. XXII, 110.

D'AVIGNON, M., HUSBY, J. and WIDEN, L. (1954).
Discussion on electroencephalographic observations in subacute progressive encephalitis.
Act. Paediatrica. 43, 111.

BABES, V. and MIRONESCO, T. (1908).
La Paralysie Ascendante Mortelle Sur Venue Apres le traitment antirabique.
C.R. Soc. Biol. Paris, 64, 964.

BAKER, A.B. (1935).
Haemorrhagic encephalitis.
Amer. J. Path. 11, 185.

BALLONIUS,
Cited by Crookshank, F.G. (1919).

BARBIER, G. (1955).
Quatre cas d'encephalites subaigues de l'enfance; Type van Bogaert.
Thesis for Doctorate in Medicine, Lille.

BARLOW, C.F. (1956).
A study of abnormal blood-brain permeability in experimental allergic encephalomyelitis.
J. Neuropath. and exp. neurol. XV. No. 2.

BASSOE /

BASSOE, P. and HASSIN, G.B. (1919).
A contribution to the histopathology of epidemic ("lethargic") encephalitis.
Arch. Neurol. & Psy. Chicago, II, 24.

BENTAL, E. (1958).
Acute psychoses due to encephalitis following Asian influenza.
Lancet II, 18.

BERNARD, L. and RENAULT, J. (1920).
L'enquête epidemiologique du ministere de l'Hygiene sur l'encephalite lethargique en France.
Bull. Acad. Med. Paris, 83, 470.

BICKERSTAFF, E.R. and CLOAKE, P.C.P. (1951).
Mesencephalitis and rhombencephalitis.
Brit. Med. J. 2, 77.

BLACK, F.L., and MELNICK, J.L. (1955).
Micro epidemiology of poliomyelitis and Herpes-B infections.
J. Immunol. 74, 3.

BOGAERT, L. van (1945).
Une leuko-encephalite sclérosante subaigue.
J. Neurol. Neurosurg. & Psychiat. 8, 101.

BOGAERT, L. van (1950).
Post-infectious encephalomyelitis and multiple sclerosis: significance of perivenous encephalomyelitis.
J. Neuropath. 9, 219.

BOGAERT, L. van (1958).
Personal communication, 5.5.58.

BOGAERT, L. van (1959).
Acute encephalitis in childhood.
Brit. Med. J. 1,1199.

BORNSTEIN, B and EFRATI, P. (1955).
Encephalomyelitis due to atypical pneumonia.
Confinia neurologica, 15, 6. 339.

BRAMWELL, E. (1921).
Discussion on encephalitis lethargica.
Brit. Med. J. 2, 648.

BREWIS, E.G. (1954).
Recent experiences of encephalitis in childhood.
Brit. Med. J. 1, 1298.

BROUWER, B. (1931).
A propes de myélite variolique.
Rev. Neurol. 2, 446.

BURNET, F.M. and LUSH, D. (1939).
Studies on experimental herpes infection in mice, using the chorio-allantoic technique.
J. Path. Bact. 49, 241.

BURNET, F.M. and WILLIAMS, S.W. (1939).
Herpes simplex; new point of view.
Med. J. Austr. 1, 637.

COLLOWER /

COLOVER, J. (1954).
Tubercule bacillus fractions in experimental allergic encephalomyelitis.
Brain 77,III, 435.

COLOVER, J. and CONSDEN, B. (1956).
Experimental allergic encephalomyelitis produced by tubercule bacillus residues.
Nature, 177, 749.

CONYBEARE, E.T. (1956).
Notified acute encephalitis (post infectious) 1950-54.
Monthly Bull. Min. of Health and Pub. Lab. Serv. 15, 40.

CRAWFORD, T. (1954).
Acute haemorrhagic leucoencephalitis.
J. Clin. Path. 7, 1.

CROOKSHANK, F.G. (1919).
The history of epidemic encephalitis in relation to influenza.
Med. Press & Circ. 2.

CROME, L. (1954).
Encephalitis during an epidemic of influenza.
Mschr. Psychiat. Neurol. 128, 159.

DAWSON, J.R. (1933).
Cellular inclusions in cerebral lesions in lethargic encephalitis.
Am. J. Path. 9, 7.

DOERR, R. and SCHNABEL, A. (1921).
Virus of febrile herpes.
Schweiz med. Wschr. 51, 469.

DOERR, R. and VOCHTING, K. (1920).
Études sur les virus de l'herpès febrile.
Rev. gen. ophtal., 34, 409.

DUFFY, C.E., PEHRSON, G.C. and MORGAN, P.N. (1952).
Interference between Japanese B. encephalitis virus and Western encephalomyelitis virus in the rat.
Proc. Soc. exp. Biol. (N.Y.) 81, 154.

DUNBAR, J.M., JAMIESON, W.M., and LANGLANDS, H.M. (1958).
Encephalitis and influenza.
Brit. Med. J. I, 913.

VON ECONOMO. (1917).
Encephalitis lethargica.
Klin. Wchn. Chr. Wien. XXX, 581.

VON ECONOMO (1931).
Encephalitis lethargica, Oxford Medical Publications.

ESPIR /

ESPIR, M.L.E. and SPALDING, J.M.K. (1956).
Three recent cases of encephalitis lethargica.
Brit. Med. J. I, 1141.

FANO, C. da (1921).
A preliminary note on the histopathology of epidemic (lethargic) encephalitis.
Brit. Med. J. I, 153.

FERRARO, A., ROIZIN, L. and CAZZULLO, C.L. (1950).
Experimental studies in allergic encephalomyelitis; Prevention and Production - note III.
J. Neuropath. exp. neurol. 9, 18.

FERRARO, A. and SCHEFFER, I.H. (1931).
Encéphalite et encéphalopathie de la rougeole.
Rev. Neurol. 2, 446.

FIELD, E.J. (1952).
Pathogenesis of herpetic encephalitis following corneal and masseteric inoculation.
J. Path. Bact. LXIV. 2.

FINLEY, K.H., LONGSHORE, W.A., PALMER, R.J., COOK, R.E. and RIGGS, N. (1955).
Western Equine and St. Louis encephalitis. Preliminary Report of a clinical follow-up study in California.
Neurology. 5, 223.

FISCHER WASELS, B. (1933).
Die funktionellen storungen des peripheren Kreislaufs.
Frank. Ztschr. f. Path. Bd. 45.

FLEXNER, S. and AMOSS, H.L. (1925).
Contributions to the pathology of experimental virus encephalitis I. An exotic strain of encephalitogenic virus.
J. exp. Med. 41, 215.

FLORMAN, A.L., MINDLIN, R.L. (1952).
Generalised herpes simplex in 11-day-old premature infant.
Amer. J. dis. child. 83, 481.

FOLEY, J. and WILLIAMS, D. (1953).
Inclusion encephalitis and its relation to subacute sclerosing leucoencephalitis.
Quart. J. Med. 22, 157.

FRANCE, N.E., and WILMERS, M.J. (1953).
Herpes simplex hepatitis and encephalitis in newborn twins.
Brit. Med. J. II, 1181.

FREUND, J., STERN, E.R. and PISANI, T.M. (1947).
Isoallergic encephalomyelitis and radiculitis in guinea pigs after one injection of brain and myobacteria in water-in-oil emulsion.
J. Immunol. 57, 179.

FRIEDENWALD /

FRIEDENWALD, J.S. (1923).
Studies in the virus of herpes simplex.
Arch. Ophthalmol. 52, 105.

FURBRINGER, P. (1892).
Zur Kenntniss schwerer organischer Hirnleiden im Gefolge von Influenza.
Dtsch. Med. Wschr. 18, 45.

GAY, F.P. and HOLDEN, M. (1931).
Loss of viricidal property in serums from patients with herpes and encephalitis.
J. Amer. med. Ass. 96, 2028.

GAY, F.P. and HOLDEN, M. (1933).
Herpes encephalitis problem.
J. infect. Dis. 53, 287.

GOODPASTURE, E.W. (1925).
Pathways of infection of central nervous system in herpetic encephalitis of rabbits contracted by contact; with comparative comment on medullary lesions in case of human poliomyelitis.
Amer. J. Path. 1, 29.

GOODPASTURE, E.W. and TEAGUE, O. (1923-4).
Transmission of virus of herpes febrilis along nerves in experimentally infected rabbits.
J. Med. Res. 44, 139.

GREENFIELD, J.G. (1930).
Acute disseminated encephalomyelitis as a sequel to "influenza".
J. Path. & Bact. 33, 453.

GREENFIELD, J.G. (1950).
Encephalitis and encephalomyelitis in England and Wales during the last decade.
Brain, 73, 141.

GREENFIELD, J.G. (1956).
Encephalomyelitis and the clinical pathologist.
J. Clin. Path. 9, 1.

GREENFIELD, J.G. (1958). Neuropathology.
Publ. Edward Arnold, London.

GRINKER, R.R. and BASSOE, P. (1931).
Disseminated encephalomyelitis. Its relation to other infections of the nervous systems.
Arch. Neurol. Psychiat. Chicago, 25, 723.

HABER /

ABER, P. (1935).
Sur un virus encéphalo-herpetique decrit sous le nom de "virus B".
C.R. Soc. Biol. Paris. 119, 136.

ALL, A.J. and YATES, A.G. (1926).
The Sheffield outbreak of Epidemic Encephalitis in 1924.
Med.res.coun.spec.Rep. No. 108. H.M. Stationery Office.

AMOEN, A.M., HERNGREEN, H., STORM van LEEUWEN, W. and MAGNUS, O. (1956).
Encéphalite subaigue progressive; constatations cliniques et electroencéphalographiques dans 23 cas.
Rev. neurol. Paris, 94, 109.

IPPOCRATES.
Epidemics. Book III. 6. (Adam's translation).

OLZEL, A., FELDMAN, G.V., TOBIN, J. O'H., and HARPER, J. (1953).
Study of complement fixing antibodies at different ages.
Acta. Pediatr. 42, 206.

URST, E.W. (1941).
Acute haemorrhagic leucoencephalitis; a previously undefined entity.
Med. J. Aust. 2, 1.

EAN de TROYES.
Cited by Crookshank, F.G. (1919).

ORDAN, R.T. and DUFFY, C.E. (1952). Interference between St. Louis Encephalitis Virus and Western Encephalomyelitis Virus along a Neuronal pathway.
J. infect. Dis. 91, 165.

ORGENSEN, M.B. (1955).
Encephalitis following Rubella.
Dan. Med. Bull. 2, 106.

UHL, D. (1921).
Beitrage zur pathologischen Anatomie der Grippe.
Virch. Arch. 232, 58.

ABAT, E.A., WOLF, A. and BEZER, A.E. (1946).
Rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of brain tissue with adjuvants.
Science, 104, 362.

ALM, H. (1952) Uber die Stellung der Panencephalitis (Pette-Doring) zur Leuccencéphalite sclérosante subaigue (van Bogaert).
Dtsch. Z. Nervenheilk. 169, 89.

APILA, C.C., KAUL, S., KAPUR, S.C., KALAYANAM, T.S. and ANERJEE, D. (1958).
Neurological and hepatic disorders associated with influenza.
Brit. Med. J. 2, 1311.

ONIGSDORF (1892). Ein neuer Fall von acuter haemorrhagischer Encephalitis wahrend der jetzigen Influenza-Epidemie.
Dtsch. Med. wschr. 18, 182.

Kopeloff /

KOPELOFF, L.M. and KOPELOFF, N. (1947).
Neurologic manifestations in laboratory animals produced by organ (adjuvant) emulsions.
J. Immunol. 57, 229.

KRISTIANSEN, K., HARKMARK, W. and COHEN, M.M. (1956).
Acute haemorrhagic encephalitis.
Neurology (Minneapolis). 6, 7.

KRUCKE, W. (1957).
Uber eine besondere Form der spontanen Encephalitis (akute, subakute und chronischrezidivierende Encephalitis) mit Einschlusskorperchen.
Nervenarzt. 28, 289.

LAUDA, E. (1923).
Der jetzige Stand der experimentellen Herpes und Encephalitisforschung.
Wien klin. Wschr. 36, 231.

LEBASCLE, J. (1956).
La leuco-encéphalite sclérosante subaigue.
Maroc. Med. 373, 35.

LEICHENSTERN, O. (1892).
Ueber primare acute haemorrhagische Encephalitis.
Dtsch. Med. Wschr. 18, 39.

LEREBOULLET and HUTINEL (1922).
Cited in pathological section of Ministry of Health Report No. 11.

LEVADITI, C. (1926).
L'herpes et le zona.
Paris.

LEVADITI, C. and HARVIER, P. (1920).
(a) C.R. Soc. Biol. Paris, 83, 354.

LEVADITI, C. and HARVIER, P. (1920).
Étude experimentale de l'encéphalite dite lethargique.
(b) Ann. Inst. Pasteur. 34, 911.

LEVADITI, C., HARVIER, P. and NICOLAU, S. (1921 (a)).
Sur la presence dans la salive des sujets sains d'un virus produisant la kerato-conjunctivite et l'encéphalite chez le lapin.
C.R. Soc. Biol. Paris, 84, 817.

LEVADITI, C., HARVIER, P. and NICOLAU, S. (1922).
Étude experimentale de l'encéphalite dite "lethargique"
Deuxieme memoire.
Ann. Inst. Pasteur. 36, 105.

LEVADITI, C. and NICOLAU, S. (1924).
Etiology of epidemic encephalitis.
C.R. Soc. Biol. Paris. 90, 1372.

LHERMITTE /

LHERMITTE (1950).
Les leucoencéphalites.
Paris.

LIEBERS, M. (1930).
Zur Histopathologie der hamorrhagischen Encephalitis bei Grippe mit akuter Hepatitis.
Z. ges Neurol. Psychiat. 126, 236.

LISITSA, F.M. (1950).
A lethargic form of encephalitis with psychotic manifestations.
Neuropat. Psikhiat. Moskva. 19, 4, 23.

LOMBARD, H.C. (1833).
Quelques observations sur la grippe qui a regne a Geneve en 1831.
Gaz. Med. de Paris. 729.

LOMBARD, H.C. (1837).
Note sur l'epidemie de grippe qui a regné a Geneve en fevrier, 1837.
Gaz. Med. de Paris, 5, 214.

MARGOLIS, M.S., SHUBLADZE, A.K. and ANDZHAPARIDZE, O.G. (1951).
The morbid anatomy and pathogenesis of experimental chronic encephalomyelitis.
Neuropat. Psikhiat. Moskva. 20. No. 2. 47.

MARINESCO, G. and DRAGANESCO, S. (1923).
Recherches expérimentales sur le neurotropism du virus herpetique.
Ann. Inst. Pasteur. 37, 753.

McCONKEY, B. and DAWS, R.A. (1958).
Neurological disorders associated with Asian influenza.
Lancet II, 15.

MEYER, E. and BYERS, R.K. (1952).
Measles encephalitis. A follow up study of sixteen patients.
Am. J. Dis. Child. 84, 543.

MINISTRY OF HEALTH (1922).
Report on Encephalitis Lethargica. Ministry of Health.
Reports on Public Health and Medical subjects.
No. 11.

MORGAN, I.M. (1946).
Allergic encephalomyelitis in monkeys in response to injection of normal monkey cord.
J. Bact. 61, 614.

MORGAN /

MORGAN, I.M. (1947).
Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue.
J. exp. Med. 85, 131.

MULLER, W. (1933).
Über einen Fall von disseminerter Leukencephalitis.
Dtsch. Z. Nervenheilk. 132, 43.

NAGLER, F.P.O. (1944).
A specific cutaneous reaction in persons infected with the virus of herpes simplex.
J. Immunol. 48, 213.

NAYRAC, P., GRAUX, P., RABACHE, R., MILBLED, G. and BARBIER, G. (1957).
La leucoencephalite sclerosante subaigue dans le Nord de la France.
Lille Medical. 3rd series. Tome II. No. 10.

NEAL, J.B. (1919).
Lethargic encephalitis.
Arch. Neurol. Psychiat. Chicago II, 271.

OZANAM, (1835).
Histoire medicale generale et particulaire des maladies epidemiques.
Paris.

PAYLING WRIGHT, G. (1956).
The Dissemination of Neurotoxins and neuroviruses in the nervous system.
Guy's Hospital Reports 105, 57.

PETTE, H. and DORING, G. (1939).
Über einheimische Panencephalomyelitis von Charakter der Encephalitis Japonica.
Dtsch. Ztsch. Nervenh. 149, 71.

PERDRAU, J.R. (1925).
Virus of encephalitis lethargica.
Brit. J. exp. Path. 6, 123.

PERRONE, H. and WRIGHT, M. (1943).
A fatal case of atypical pneumonia with encephalitis.
Brit. med. J. II, 63.

PETTE, H. (1936).
Post vaccinale encephalitis.
Bumke and Foersters Handbuck der. Neurol. Vol. 13, 259.
Berlin.

RADERMECKER /

RADERMECKER, J., LOWENTHAL, A., MACKEN, J. and MEULDERS, M.(1957).
Meningo-encéphalites aigues d'origine indeterminée a forte composante psychique et à evolution favorable.
Rev. Neurol. 97, 21.

RANKIN, N.E. and DANCE, J. (1956).
Case of acute haemorrhagic leuco-encephalitis.
Brit. Med. J. II, 808.

RECORDIER, M., GASTAUT, H., BOGAERT, van L. and RADERMECKER, J. (1956). Remarques sur une nouvelle observation d'encéphalite necrosante aigue avec inclusions.
Rev. Neurol. 95, 116.

REYNOLDS, F.E. and SLATER, J.K. (1929-30).
A contribution to the pathology of the later manifestations of encephalitis lethargica: investigation of a case.
J. Neurol. Psychopath. 10, 242.

VAN ROOYEN, C.E. and RHODES, A.J. (1948).
Virus diseases of man.
Thomas Nelson & Sons, New York.

ROSS, C.A.C. and STEVENSON, J. (1961).
Herpes simplex meningo-encephalitis.
Lancet. 2, 682.

ROSTAN, A. (1930).
Contributo alla patologia dell'encefalite influenzale.
Riv. di Neurol. 3, 146.

SABIN, A.B. (1934).
Studies on B virus; experimental disease in Macacus rhesus monkeys.
Brit. J. exp. Path. 15, 321.

SABIN, A.B. and WRIGHT, A.M. (1934).
Acute ascending myelitis following a monkey bite with isolation of a virus capable of reproducing this disease.
J. exp. Med. 59, 115.

SCHLEISNER, P., THORSTEINSSON, J. and BOGESKOV-JENSEN, L. (1955).
Rubella-encephalitis.
Dan. Med. Bull. 2, 101.

SCHNABEL, A. (1922).
Relation between virus of encephalitis and of herpes febrilis.
Klin. Wschr. 1685.

SHAPOVAL, A.N. and SARMANOVA, E.S. (1955).
A peculiar form of encephalomyelitis.
Klin. med. (Mosk.) 33, 75.

SMITH, H.F. (1921).
Epidemic encephalitis (encephalitis lethargica, Nona).
Report of studies conducted in the United States.
Publ. Hlth. Rep. Wash. 36, 207.

SMITH /

SMITH, M.G., LENNETTE, E.H. and REAMES, H.R. (1941).
Isolation of the virus of H. simplex and the demonstration of intranuclear inclusions in a case of acute encephalitis.
Am. J. Path. 17, 55.

SOSA MARTINEZ, J., and LENETTE, E.H. (1955).
Studies on complement fixation test for Herpes simplex.

SOUTHCOTT, R.V. and FOWLER, M. (1954).
A further case of acute haemorrhagic leucoencephalitis (Hurst).
Med. J. Aust. 65.

STEPHENS, J.H. (1957).
Haemorrhagic leuco-encephalitis.
Scot. Med. J. 2, 154.

STILL, R.M.L. (1958).
Psychosis following Asian influenza in Barbados.
Lancet II, 20.

STRAUSSLER, E. (1902).
Zur Aetiologie der acuten hamorrhagischen Encephalitis.
Wien. Klin. Wschr. 15, 61.

STRUMPELL, A. (1891).
Uber primare acute Encephalitis.
Dtsch. Arch. klin. med. 47, 53.

TERAI, H. (1955).
Studies on experimental allergic encephalitis.
Fol. psych. Neurol. Jap. 9, 20.

THOMSON, T. (1852).
Annals of influenza or epidemic catarrhal fever in Great Britain.
Sydenham Society Publication, London.

TROUP, A.G. and HURST, E.W. (1930).
Disseminated encephalomyelitis following smallpox.
With report of a fatal case.
Lancet, I, 566.

TURNBULL, H.M. and McINTOSH, I. (1926).
Encephalomyelitis following vaccination.
Brit. J. exp. Path. 7, 181.

WALSHE, F.M.R. (1920).
On the symptom-complexes of lethargic encephalitis with special reference to involuntary muscular contractions.
Brain, 43, 197.

WHITMAN, L., WALL, M.J. and WARREN, J. (1946).
Herpes simplex encephalitis; a report of two fatal cases.
J.A.M.A. 131, 1408.

WILDI /

WILDI, E. (1951).
Herpetic encephalitis of the newborn.
Rev. Neurol. 84, 201.

WILDY, N.P.L. (1955).
Unpublished work cited by Payling Wright (1956).

WOLFF, K. (1937).
Beitrag zur Morphologie der Kreislaufstorungen im Gehirn.
Bau und Entstehung der Ringblutungen.
Virch. Arch. Path. Anat. u. Physiol. Bd. 298, 98.

ZARAFONETIS, C.J.D., SMADEL, J.E., ADAMS, J.W. and HAYMAKER, W. (1944).
Fatal H. simplex encephalitis in man.
Am. J. Path. 20, 429.

ZEVIANI, (1804).
Sul catarro epidemico. Memorie di matamatica e di Fisica della Societa Italiana delle Scienze.
XI. p. 476.

ZINSSER, H. (1928).
General Review. The present state of knowledge regarding epidemic encephalitis.
Arch. Path. 6, 271.

APPENDIX

CASE HISTORIES

GREENOCK.	GROUP A	CASES	1 - 7.
	GROUP B	CASES	8 - 10.
GLASGOW.	GROUP C	CASES	11 and 12.
	GROUP D	CASES	13 - 18.

All cases are arranged in chronological order.

CASE HISTORIES

GREENOCK. GROUP A CASES 1 - 7

CASE 1. (First admission).

Sex: Female.

Age: 20 years.

Complaint

6.8.57. The patient awakened and began to cry out with the pain of intense frontal headache. The pain was accompanied by nausea but not by vomiting. She had gone to bed in normal health on the previous night. Menstruation had started some hours before the onset of headache.

Previous history

The patient was a young housewife. A year previously she had given birth to a normal infant at full term. Pregnancy and parturition had been uneventful and the child had progressed normally in infancy. The patient had had measles and whooping cough as a child and she had been vaccinated and immunised against diphtheria in her early years. In June 1950, at the age of thirteen years, she had acute appendicitis and was treated by appendicectomy from which operation she made a normal recovery. Soon after puberty she complained of dysmenorrhoea and as this was a recurrent disability she was referred for gynaecological opinion in 1954. The report at this time indicated that the reproductive organs were normal. The patient however still continued to complain intermittently of painful menstruation although the cycle was regular and normal. In 1955 the patient, now aged eighteen years, was affected by nasal catarrh and troublesome cough. Physical

examination /

examination and x-ray examination of the thorax did not reveal any significant lesions. The Mantoux test was positive at this time. There was no history of ear trouble.

State on admission

The patient was a young woman of good nutrition and normal development. Temperature 97°F; pulse 64/min; respiration 32/min. Apart from the presence of severe headache physical examination did not reveal any sign of organic disease. In particular, all findings in the examination of the nervous system were within normal limits. Shortly after admission a second complaint of pain was made. This was located in the back and radiated to the occiput.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
6.8.57.	2/cu.mm.	N/A	20 mg%	N/A

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.
6.8.57.	13.4 gm%	35	38%	5,500/cu.mm.

Widal)
Paul Bunnell) Reactions normal.

Catheter specimen of urine:-

Neither blood cells nor casts were present.
Scanty squames and a few oxalate crystals were seen.

Bacteriology:-

Throat swab: Mixed buccal flora.

Nasal swab: Mixed normal commensal flora.

Progress /

Progress

On the day of admission the headache began to improve and within twelve hours had completely disappeared. The patient had no further complaints and was feeling perfectly well. She was discharged two days later (8.8.57).

CASE 2.

Sex: Female.

Age: 20 years.

Complaint

26.8.57. The patient, a previously healthy young woman, complained of stiffness and pain in the back of the neck accompanied intermittently by vomiting. The pain persisted for four days and became worse spreading to the vertex. The patient continued to vomit intermittently.

Previous history

The patient, a Borstal inmate, was six months pregnant. She had been well until the onset of the present illness. Immunisation against any infectious disease had not been effected in childhood.

State on admission

30.8.57. The patient was a young woman six months pregnant. Temperature 97°F; pulse 120/min; respiration 24/min.

The positive findings on examination were slight. A soft systolic murmur was present at the base of the heart and the second heart sound in the pulmonary area was slapping in quality. The blood pressure was 115/60 mm.Hg. Examination of the genito-urinary system disclosed a uterus enlarged within normal limits for a pregnancy of six months duration. Albumin was not present in the urine.

Examination of the nervous system revealed the presence /

presence of slight nuchal rigidity but all other findings, including auroscopy, were within normal limits.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
30.8.57.	2/cu.mm.	N/A	20 mg%	N/A

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.
2.9.57.	9.8 gm%	29	34%	5,500/cu.mm.

Bacteriology:-

Vaginal smear: Negative for pathogens.

Stools : Thread worms present.

Progress

Five days after admission (4.9.57) all symptoms had cleared and the patient was feeling perfectly well. She was discharged from hospital on 10.9.57. The patient remained well, and, following the usual practice, was discharged from Borstal to a maternity home at the approach of term. The patient was delivered of a normal full term infant and both mother and child have remained well to date.

CASE 3.

Sex: Male.

Age: 24 years.

Complaint

15.9.57. The patient, an able seaman on active service in the Royal Navy, complained of severe frontal headache, sore throat, cough and general malaise.

Previous history

The patient had had whooping cough and chicken pox in childhood and he had been vaccinated and immunised against diphtheria. He had also received B.C.G. He was in good health up to the onset of the present illness and had not been recently in contact with known infectious disease.

State on admission

16.9.57. The patient was a young man of good nutrition described as "toxic looking". The positive findings in the respiratory system were confined to the pharynx and fauces which were inflamed and oedematous. Examination of the nervous system revealed a positive Kernig's sign and slight nuchal rigidity. All other findings were within normal physiological limits.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
16.9.57.	1/cu.mm.	N/A	50 mg%	N/A

Blood /

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.
16.9.57.	15.6 gm%	52	30%	7,000/cu.mm.

Bacteriology:-

H. influenzae and numerous pneumococci were present in material from throat swab and sputum.

Blood culture was sterile after three weeks incubation.

Progress

Forty eight hours after admission the patient was afebrile and did not have any complaints. He was discharged to duty six days after admission (21.9.57). The patient has remained well to date.

CASE 4.

Sex: Male.

Age: 15 years.

Complaint

25.9.57. Towards the end of September 1957 behaviour disorders in the patient were observed by the parents who sought medical advice.

Previous history

The patient was the second of a family of three children and was born after a normal pregnancy and confinement. The patient developed normally in childhood and although he contracted both measles and whooping cough, he made normal recoveries from these ailments. At the age of six he was admitted to a cottage hospital in England with a diagnosis of tabes mesenterica and was discharged after remaining a month in hospital. Records of investigations made at the time of this illness were not available on enquiry.

The patient's medical history after this date was unremarkable. A few weeks before the onset of influenza in September 1957 the patient had attended an interview for admission to the Royal Naval College, Dartmouth. In this, he had been unsuccessful but he was unaware of the result as the news was not received by his family until after his admission to hospital at the end of September 1957.

Early in September 1957 several members of the patient's family including his parents and sisters suffered from an acute /

acute febrile respiratory illness diagnosed as influenza. About the middle of the month the patient began to show the same symptoms; he complained of sore throat and cough in all respects similar to those experienced earlier by other members of the family and a diagnosis of influenza was made in his case. He also complained of severe headache and nausea but did not vomit. Until 20.9.57 the illness ran a normal course and the patient appeared to be improving. On 21.9.57 the patient's father was concerned to observe that his son remained immobile and uninterested in his surroundings. On questioning, the patient failed to give intelligent replies and he remained in this withdrawn state for forty eight hours when he showed a little improvement. On the following day (24.9.57) he complained of double vision and began abusing his parents and spitting in bed.

State on admission

27.9.57. The patient was a well nourished boy of good average physical development for his years. The only positive objective finding in general physical examination was of slight faucial congestion. Examination of the central nervous system was negative for signs of organic disease except that although nuchal rigidity as such was not present the patient was unable fully to flex his head on his trunk.

Investigations /

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
27.9.57.	1/cu.mm.	750 mg%	20 mg%	68 mg%

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.	E.S.R.
27.9.57.	16.8 gm%	47	30%	6,100/cu.mm.	2 mm 1st hour Wintrobe

Bacteriology:-

28.9.57. Throat swab: Heavy mixed buccal flora on culture including some beta-haemolytic streptococci.

Progress

Throughout his stay in hospital the patient was fully orientated and did not display either hallucinations or delusions, but in conversation, the manner of his replies even to simple questions was abnormal. While his answers were basically correct the replies were framed in such a manner as best to score off the questioner. His general attitude during interrogation was sly and gave the impression of aggressive insolence. When left alone he talked in a childish manner to other patients in the ward. He made no complaint and took his food well. His mental state was very variable and in his worst moods he sang bawdy songs and made improper suggestions to the nurses and exposed himself sexually to them. He gave the impression that he was aware of what he was doing on these occasions but wished to shock his audience.

The /

The patient frequently displayed extreme restlessness in bed and often required to be restrained from wandering about the wards at night although he was at all times fully orientated. From time to time sedation by paraldehyde was required.

A week after admission his mental state was unchanged and the patient was discharged to a mental hospital (4.10.57). While in this institution he was questioned about spitting freely and he replied that he was obliged to get rid of saliva which kept filling his mouth. At the same time it was noticed that he tended to walk in circles to the right. The patient remained in this hospital for twenty four hours before being removed at his parent's request to a private mental institution. On admission he was mentally clear and rational but had difficulty in concentration and a tendency to emotional reactions of a compulsive character. He had only a faint partial recollection of the psychotic period of his illness. Psychiatric opinion in both mental hospitals favoured the view that this patient's psychosis had resulted from an encephalitic illness.

The patient was discharged on 26.10.57 and returned home when all disorders had apparently been resolved.

He was examined again on 19.2.58 and found to be free of the disorders of behaviour previously noted. His general attitude was cooperative and his mood brisk and confident. At this time he had returned to school and was interested in his studies and games and was making good progress. The patient's father questioned privately on this date was of the opinion /

opinion that complete recovery had taken place. He thought, however, that his son had matured rapidly and whereas he had had a boyish outlook before his illness his attitude at this date was more adult. The only positive findings on neurological examination were that the reflexes in both lower limbs were very brisk and could be elicited with light finger tap. These changes were more marked in the left than in the right leg. Clonus, which was not sustained, was readily elicited, especially in the left leg.

A few days after this examination the patient became morose and made irrational replies to simple questions. He was not, however, aggressive but seemed confused. He remained in this state for four days and thereafter became quite rational. On recovery, he had no memory of this irrational episode.

CASE 5.

Sex: Male.

Age: 17 years.

Complaint

3.12.57. The patient complained of severe frontal headache and general malaise accompanied by nausea. The headache persisted on the following day and was accompanied by vomiting.

Previous history

The patient, an apprentice draughtsman, had not recently been in known contact with infectious disease. He had had chicken pox in childhood and had been immunised against smallpox, diphtheria, whooping cough and tuberculosis. In September 1956 he had suffered a respiratory disorder which was regarded radiologically as a primary atypical pneumonia; his father and mother were similarly affected at intervals of a few months. In September 1957 the patient was reported to have sustained a head injury which was followed by transient blindness lasting a few seconds. On this occasion the patient did not seek medical advice.

State on admission

5.12.57. Temperature 101°F; pulse 90/min; respiration 24/min. The patient was a well nourished youth of fair average development. He was semicomatose and could be roused only with difficulty. He showed marked neck stiffness and Kernig's sign /

sign was bilaterally positive. All abdominal reflexes were absent; all others were brisk and equal on both sides. The pupils were small and equal and reacted sluggishly to light.

Investigations:-

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
5.12.57.	38/cu.mm. Lymphocytes.	680 mg%	50 mg%	74 mg%
6.12.57.	30/cu.mm. Lymphocytes.	700 mg%	50 mg%	81 mg%
7.12.57.	64/cu.mm. Lymphocytes.	700 mg%	45 mg%	86 mg%

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.	Blood Urea	Blood sugar
5.12.57.	14.3 gm%	42	34%	9,200/cu.mm.	-	128 mg%
6.12.57.	15.4 gm%	50	31%	5,700/cu.mm.	-	-
7.12.57.	-	-	-	-	56 mg%	-

Bacteriology:-

Urine - Culture: Heavy growth of B. Proteus vulgaris sensitive to chloramphenicol and streptomycin.

Progress

6.12.57. The day after admission the patient developed a right facial palsy; he was just able to speak but was very confused. Later that day jerky movements began in the left shoulder. The eyes were now deviated to the left and Jacksonian twitching developed in the left hand and arm. On the left side the plantar response was extensor; on the right it /

it was flexor. Marked neck stiffness was evident; clonus was not elicited but the musculature generally was slightly spastic. The pupils were small and unequal and they reacted very sluggishly to light. Examination of the fundi showed blurring of the nasal margins of the discs and this was more noticeable in the left eye. During the day the patient's temperature rose from 101°F. to 104°F. and his pulse rate increased from 110/min to 130 min. A course of intramuscular penicillin was initiated.

On the following day the patient was comatose with very marked neck stiffness and right facial paresis. The left arm was spastic and exhibited continuous clonus. This limb was held in spastic flexion with the hand in main d'accoucheur position.

The patient's condition was unchanged during the next three days. He was catheterised daily and from 1,170 to 1,230 mls. of urine were removed on each occasion. On the following day rapid deterioration was evident and death occurred (12.12.57).

Necropsy (Seventeen hours after death).

The body was that of a youth of fair muscular development. The only positive findings in the body other than those in the central nervous system were of bilateral pulmonary congestion and oedema most marked in the lower lobes. The kidneys were of normal shape and size but were severely congested. The liver and spleen showed similar but less well marked /

marked changes. The urinary bladder was distended and the contained urine was opaque.

The scalp and skull were healthy. Middle ear disease was not present and the frontal sinuses were normal. The dura was under slightly increased tension and the cerebral hemispheres bulged slightly when this membrane was incised. The cerebrum superficially was dry and fitted the cranial cavity exactly. The superficial vessels of the cerebral hemispheres were congested but the vessels at the base of the brain showed normal appearances. Section at the level of the upper margin of the pons disclosed pink striation in the white matter disposed symmetrically on both sides. Section of the hemispheres revealed marked generalised congestion throughout the white matter of the centrum ovale with scattered areas of punctate haemorrhage. At a lower level, similar lesions were apparent in the putamen and thalamus (Figs. 1 and 2). The lateral ventricles and aqueduct appeared macroscopically normal.

Morbid histology

Venous and capillary congestion was present in the leptomeninges in many areas and often this was associated with a proteinous exudate containing numerous cells. In many fields in the leptomeninges infiltrating cells were not confined strictly to the immediate zone about the vessels but were fairly widely dispersed. In the subarachnoid space plasma cells and lymphocytes were present in large numbers and varying /

varying proportions in contrast to the cellular infiltrate within the brain where the cells were almost exclusively lymphocytes. The morbid histological features of the leptomeninges were constant in type throughout but the exudate varied in cellular content in different parts of the central nervous system. Sections from the cervical cord showed normal appearances but venous congestion was apparent over the upper part of the medulla. At the level of the pons, venous congestion was marked and was accompanied by a cellular infiltrate in which lymphocytes were predominant. These features were repeated in sections from the mid brain and were fully developed over both cerebral hemispheres. The most florid examples were seen in sections from the temporal lobes and these were most marked over the right temporal pole (Fig. 3).

The lesions in the central nervous system were largely confined to veins and their immediate surroundings; the arteries throughout appeared normal. Widespread venous congestion with perivenous lymphocytic cuffing was the most common feature. Within the brain, lesions were most numerous and most severe in the white matter; they were present only rarely in the grey matter and were always less conspicuous. Where the lesions were slight or moderate, veins and venules were affected, but where they were severe, capillaries also were included in the morbid process. Endothelial swelling was not seen in the larger veins but, in the most severely affected areas, the venules and capillaries frequently displayed /

displayed this feature, and, in some instances, this change had progressed to the point of capillary necrosis with associated haemorrhage. Within the substance of the brain, perivascular cuffing was strictly limited to the Virchow Robin spaces and the infiltrating cells were almost exclusively lymphocytes. The brain tissue surrounding the vessels was not infiltrated by inflammatory cells except in the comparatively rare instances of vascular necrosis. Polymorphonuclear leucocytes were very rarely observed at the sites of lesions and extravasations of erythrocytes were also very infrequent. The few small haemorrhages seen showed neither ring nor ball forms (Fig. 4). Demyelination was not a conspicuous feature in this case. When present, it was localised and confined to a small perivascular area. This change was not observed in areas unassociated with vessels.

At the level of the gracile and cuneate nuclei within the medulla slight venous congestion with moderate endothelial swelling in the venules was seen in vessels in the nuclear masses. A slight perivenous infiltrate of lymphocytes was associated with these changes. The vessels of the white matter at this level showed similar but more marked changes with moderate cellular infiltrate. Demyelination was not observed in association with these changes. Within the pons venous changes in the nuclear masses were similar but more severe. The vascular lesions of the white matter at this level were well marked and included marked congestion and perivenous /

perivenous cellular cuffing. Small isolated examples of capillary breakdown with haemorrhage were also present at this level and small aggregations of microglial nuclei were apparent sometimes in relation to the smaller vessels and sometimes in areas apparently remote from vascular damage (Fig. 4). Circumscribed perivascular zones of sharply limited demyelination were also occasionally present (Fig. 5).

Changes in the vessels of the right cerebellar hemisphere were very slight and in the cortex were confined to congestion. These were within probable normal post mortem limits. A few veins in the white matter showed fairly marked congestion and some of these were sparsely cuffed with lymphocytes. Within the left cerebellar hemisphere moderate venous congestion was evident in the cortex but vascular changes within the white matter included marked congestion and cellular cuffing. Small areas of increased microglial density were seen in relation to some of the affected vessels (Fig. 6).

At the bases of the cerebral hemispheres the veins of the nuclear masses again were congested and cuffed by cells (Fig. 7) and on the left side this cuffing was dense (Fig. 8). Areas of white matter in this region showed similar changes but the most severe lesions were found in zones closely adjacent to the basal nuclei. The ependyma of the third ventricle was normal but venous lesions of moderate severity were occasionally present in the sub-ependymal region.

Sections from the frontal, parietal, temporal and occipital /

occipital lobes of the cerebrum displayed throughout features similar to those already described, but the lesions were always most marked in the white matter and were much less severe in the cortex. Many sections showed only very slight cortical changes which might be regarded as acceptable within normal limits. The most severe changes were seen in sections from the middle gyrus of the right temporal lobe. The white matter showed also a moderate but generally dispersed increase in numbers of microglial nuclei and early demyelination was apparent in the more severely affected areas (Figs. 9 and 10). In many sections from the left cerebral hemisphere venous congestion and cellular cuffing were most severe in the sub-cortical region (Fig. 11). The ependymal lining of the lateral ventricles was healthy although venous congestion sometimes accompanied by cuffing was seen in some areas.

Inclusion bodies were not observed either in nerve cells or glial cells in any of the sections examined.

CASE 5

FIGURES 1 - 11

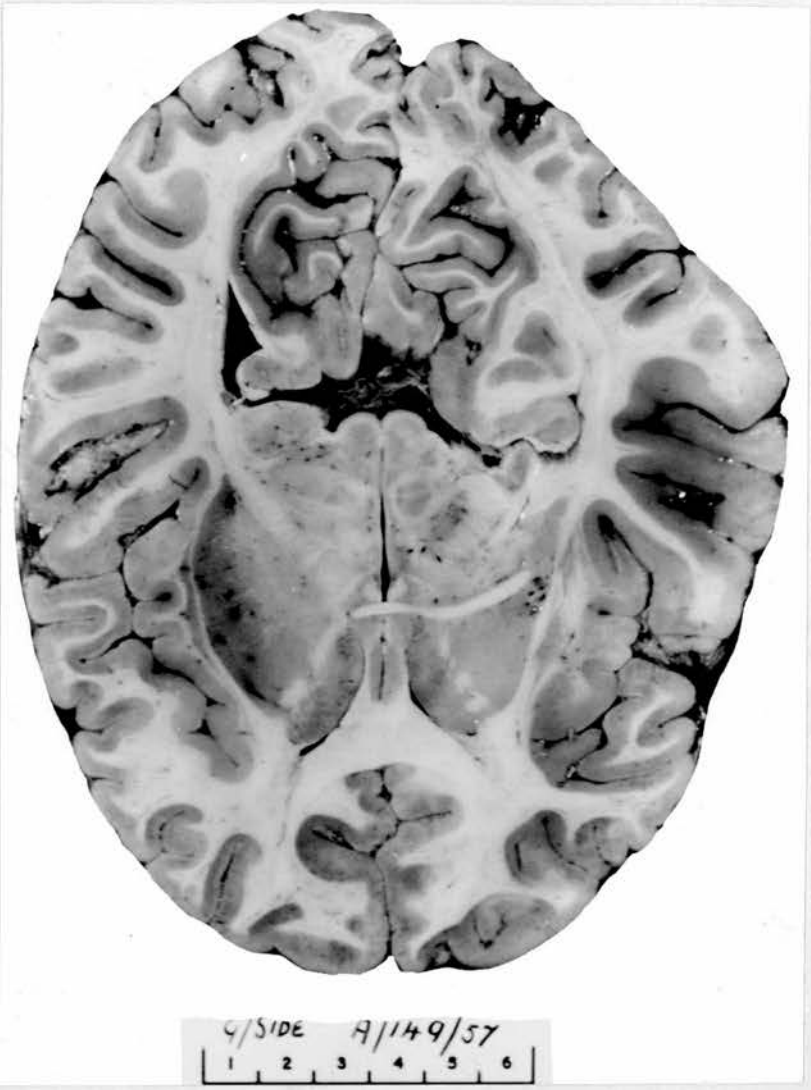

Fig. (1) Cerebrum. The bilateral distribution of punctate haemorrhagic lesions is evident in the cerebral hemispheres.

Fig. (2) Cerebrum; detail of Fig. (1). The figure illustrates the distribution of vascular lesions in the thalamus of the right cerebral hemisphere.

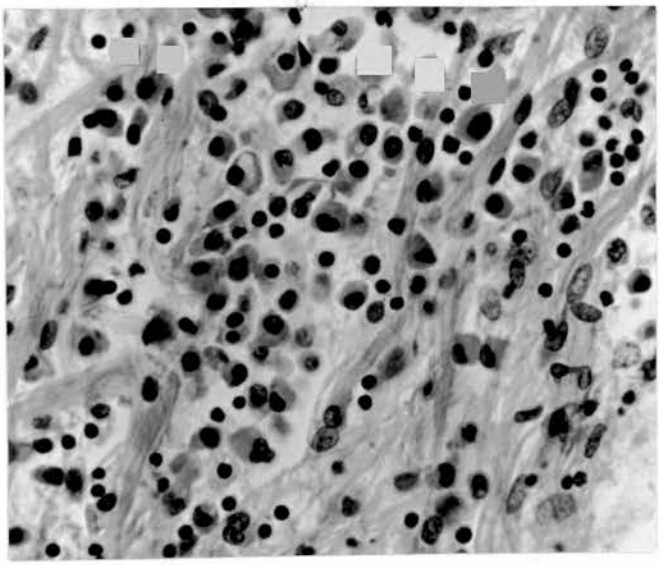

Fig. (3) Leptomeninges of the right temporal lobe.
Plasma cells and lymphocytes are present in the cellular infiltrate.
Haemalum and eosin; (X430).

Fig. (4) Lower pons.
Small irregular haemorrhages are present in the white matter and nearby are congested venules. Under higher magnification, these vessels show lymphocytic cuffing and early necrosis.
Haemalum and eosin; (X55).

Fig. (5) Lower pons.
Small congested veins are surrounded by zones of demyelination.
Loyez; (X55).

Fig. (6) White matter of the left cerebellar hemisphere.
Congested veins display moderate lymphocytic perivenous infiltration. An increase in the number of microglial nuclei is apparent about some of the vessels.
Haemalum and eosin; (X55).

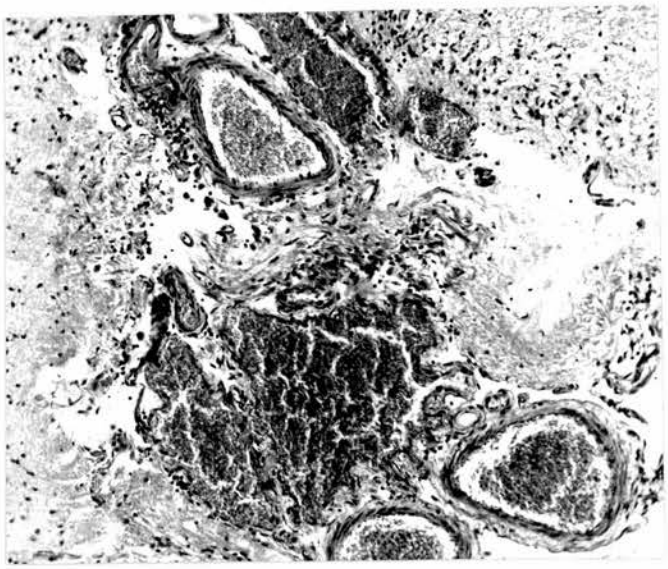

Fig. (7) Left cerebral hemisphere; posterior perforated substance.
A leash of vessels shows congestion and associated proteinous exudate.
Haemalum and eosin; (X105).

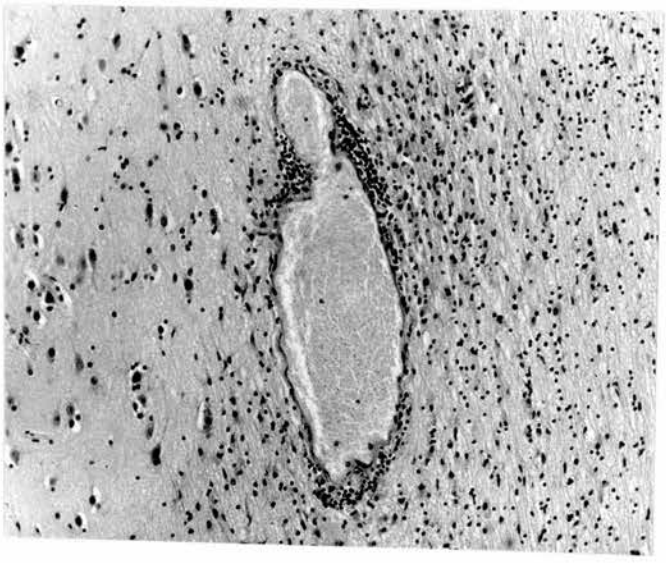

Fig. (8) Thalamus of the left side.
A congested vein displays perivenous lymphocytic infiltrate.
Haemalum and eosin; (X105).

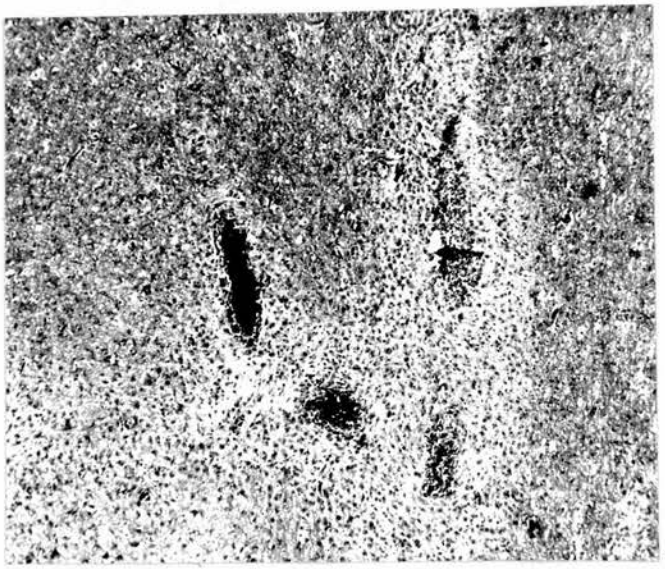

Fig. (9) White matter of the right temporal lobe.
Early demyelination is evident about several small veins.
Loyez; (X55).

Fig. (10) White matter of the right temporal lobe.
A dense perivenous cuff of lymphocytes is surrounded by a zone of microglial proliferation.
At a higher magnification the changes of early demyelination are evident.
Haemalum and eosin; (X55).

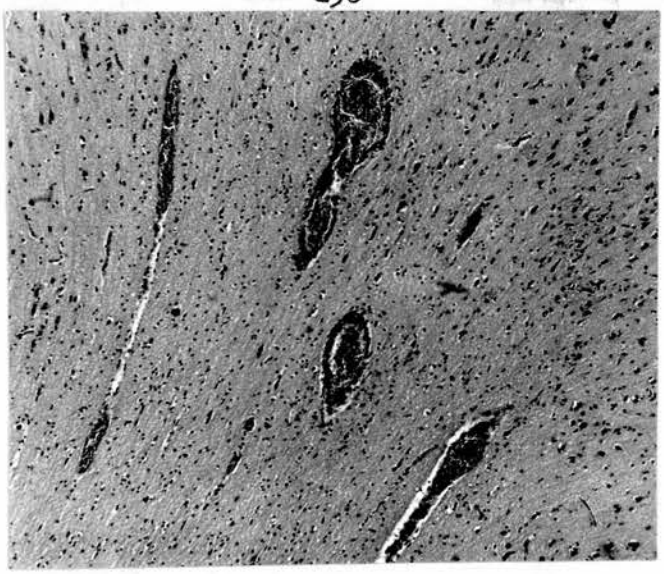

Fig. (11) Subcortical white matter of the left cerebral hemisphere.
Severe venous congestion with lymphocytic cuffing is present.
Haemalum and eosin; (X65).

CASE 6.

Sex: Male.

Age: 6 years.

Complaint

10.1.58. The patient had shown restlessness, irritability and purposeless movements of the limbs for about one week.

Previous history

The patient had been a full term baby and had developed normally in infancy. A history of convulsive attacks in infancy was not obtained. The patient was vaccinated and given B.C.G. in infancy and he was also immunised against diphtheria and whooping cough.

He first attended school at the age of five and throughout his stay in school was in the charge of the same mistress who regarded him as a timid child of average ability. In 1956 and 1957 the patient had had attacks of tonsillitis from which he made uneventful recoveries. He did not have any other illnesses until October 1957 when he developed a febrile illness diagnosed as Asian influenza. On this occasion he was absent from school for a few days and on his return his school mistress noticed that he was detached in manner and responded abruptly when called by name. He was observed to be withdrawn and he did not talk voluntarily to other children, nor did he play with them. His responses to the spoken word became increasingly /

increasingly more slow and the rapid decline in his mental state was reflected in his new position at the bottom of his class. At the same time it was observed that he did not ask to be excused to go to the toilet and on occasion he was incontinent of urine in the classroom. Although he had been regarded as a clumsy child it was now observed that he was stumbling and falling very often and on one occasion he received a severe cut as the result of a fall. The school mistress drew the parents' attention to the profound change in the child's condition. Early in December 1957 he began to show changes in behaviour described as shouting and laughing very readily and with little reason. These changes persisted until the onset of restlessness, irritability and purposeless movements of the limbs in January 1958.

The patient's two brothers also attending the same school were described as average normal children.

State on admission

10.1.58. The patient was a fairly well nourished small boy. He was conscious but drowsy and disorientated.

The only positive findings on physical examination other than those in the central nervous system were of large but not inflamed tonsils.

Examination of the central nervous system did not reveal nuchal rigidity and Kernig's sign was negative. The pupils were equal and reacted normally to light. A right sided facial paresis was present and both the right arm and right /

right leg were spastic and showed coarse spastic tremor. The abdominal reflexes were all present but the right knee jerk was not elicited.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
10.1.58.	14/cu.mm.	720 mg%	75 mg%	77 mg%
15.1.58.	4 nucleated cells) 40 R.B.Cs.)	720 mg%	50 mg%	97 mg%
1.2.58.	1/cu.mm.	720 mg%	30 mg%	83 mg%
12.6.58.	1/cu.mm.	720 mg%	30 mg%	108 mg%

Colloidal Gold test: 5555430.

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.
10.1.58.	14.1 gm%	43	33%	6,100/cu.mm.

Bacteriology:-

Examination of specimens from pharynx, throat, rectum, urine and faeces did not yield any significant growth.

Virology:-

Negative results were given by inoculation of monkey tissue cultures with stool (16.1.58, 23.1.58 and 5.2.58), throat swab and cerebrospinal fluid (21.1.58).

Negative results were given by inoculation of HeLa tissue cultures with plasma and blood cells (21.1.58).

Negative results were obtained from intracerebral inoculation of adult mice with cerebrospinal fluid, plasma, blood cells and extract of blood clot (21.1.58).

Progress /

Progress

The patient remained drowsy after admission to hospital. He could not be roused to answer questions properly but sometimes responded with either "Aye" or "O.K.". These were the only words he was heard to utter. The right sided spasticity noted on admission persisted and the right arm was held in flexion and the right leg in extension. Clonic movements were elicited on stimulation but stretch clonus was not obtained. Incoordinated movements of the left arm and leg were observed from time to time.

Ten days after admission the patient no longer responded with words but screamed in response to any disturbance or examination. About this time also he was observed to grind his jaws forcibly and this pattern of behaviour was maintained. A fortnight after admission (24.1.58) all four limbs were spastic and those on the left showed "lead-pipe" type of spasticity. Still later (1.2.58) spasticity passed off from the right arm and leg which now were spontaneously moved without stimulus. The limbs of the left side remained rigidly spastic.

Early in February the patient began to deteriorate. Mild pyrexia developed and was maintained for several days; at the same time the patient was sweating freely. Examination provoked very irritable responses with screaming and the patient was difficult to feed. The general neurological signs in the limbs remained the same. The attitude of spastic extension /

extension in the lower limbs and spastic flexion of the upper limbs was characteristic at this period. The reflexes were variable from day to day but the plantar reflexes were often extensor. In mid February the general condition of the patient had improved and he was afebrile and was eating and drinking well. The general neurological state remained substantially unaltered although the plantar reflexes on occasion were flexor.

The patient remained in the same state with minor variations in attitude and degree of irritability for the following few weeks. On 13.3.58 both upper and lower limbs on the right side were held in spastic flexion while those on the left were in spastic extension. The head and eyes on this date were deviated to the right. Both plantar reflexes were flexor. Early in April marked head retraction was a new feature in the general attitude of the patient and at this time occasional vomiting was a troublesome complication. Head retraction persisted and opisthotonos became gradually established so that by the end of April this was a constant feature. Periodically the patient sweated profusely. Early in May the pattern of limb posture became fixed with both upper limbs and the right lower limb held in spastic flexion and the left lower limb in spastic extension (Fig. 1). The reflexes at this time were normal although abdominal reflexes were not elicited.

The patient remained virtually unchanged for a period of nine months during which time he survived only by virtue of good nursing. He was transferred to a hospital for chronic patients on 12.3.59 and a week later succumbed to pneumonia. Permission for necropsy was not obtained.

CASE 6

FIGURE 1

Fig. (1) The figure illustrates the characteristic posture of the patient (April 1958) with both upper limbs and right lower limb held in spastic flexion; the left lower limb is in spastic extension. Head retraction is evident and the patient is screaming.

CASE 7.

Sex: Male.

Age: 33 years.

Complaint

25.1.58. The patient was brought home from his work complaining of persistent headache, shivering and malaise. He was confined to bed and his condition steadily deteriorated.

Previous history

The patient was born after an uneventful pregnancy and labour. He developed normally in infancy and childhood and suffered only mild attacks of measles and scarlet fever in his early years.

The patient was on active service in the Army during the war of 1939-45 and was abroad for part of this time. He suffered snake-bite in Mombasa in 1941 and in 1945 contracted malaria which recurred once in 1948.

About 20.1.58 the patient complained of the onset of an illness resembling influenza. Two days later he was exposed to a downpour of rain and on the following day he complained of severe shivering. He remained at work until 25.1.58 when he collapsed. Before admission to hospital on 30.1.58 the patient was confined to bed at home and was given aspirin and Dover's powder on 27.1.58. On this day a transient rash was observed on the patient's neck and chest but it had disappeared within twenty four hours. A course of intramuscular penicillin was initiated on 29.1.58.

The /

The patient did not exhibit the signs of herpes simplex of the face or penis at any time during his fatal illness nor had this disease appeared in anyone recently associated with him.

State on admission

30.1.58. Temperature 95°F; pulse 110/min; respiration 24/min. The patient was a well nourished man, lying comatose in bed with eyes and face turned to the right. The only positive findings on general physical examination, other than those in the central nervous system, were of furring of the tongue and scattered ronchi audible in both lung fields. The blood pressure was 136/80 mm.Hg.

Marked neck stiffness was evident and flaccid weakness was apparent in all limbs. All reflexes were present in both arms and legs and they were brisk and equal on both sides; abdominal reflexes were absent and plantar responses were equivocal. The patient did not respond to painful stimulation. The left pupil was slightly larger than the right but both reacted to light; examination of the fundi showed cupping of the discs.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
30.1.58.	52/cu.mm. mainly polymorphs.	740 mg%	20 mg%	91 mg%

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.	Sugar	Urea
30.1.58.	15.9 gm%	50	32%	7,000/cu.mm.	170 mg%	76 mg%

Virology:- Specimens removed from the brain were investigated and herpes simplex was isolated from the mid brain.

Progress

The patient remained comatose but occasionally his expression suggested that he was aware of his surroundings. The head and eyes remained turned to the right until death four days later.

The pupils remained unequal, the left larger than the right. Extraocular cranial nerve palsies were not detected and did not develop in the course of the illness. Response to painful stimulus at all times was either absent or minimal. The left arm was held in flexion and occasional movements were made with this limb in the direction of the mouth and these appeared to be purposeful although they were accompanied by coarse tremor. In the last forty-eight hours of life the patient passed into an apparent state of trance with eyes open and directed to the right. The reflexes elicited throughout the illness were very variable.

The general condition of the patient deteriorated steadily and he died without return of consciousness on 3.2.58.

Necropsy (Two hours after death)

The body was that of a spare muscular man. The positive findings apart from those in the central nervous system were confined to the lungs. Congestion, oedema and consolidation were evident at both pulmonary bases but were more marked on the right side than on the left. Acute inflammatory changes were present in the trachea and larger bronchi.

The scalp, and skull were healthy. The dura was under increased /

increased tension and the hemispheres bulged on incision of this membrane. The superficial vessels of both hemispheres were intensely congested. The surface of the brain generally was dry.

The brain was sectioned with sterile precautions and portions of tissue were removed for virological examination from the right hemisphere, mid brain, pons, medulla and thoracic cord.

The cut surface of the pons showed intense congestion with petechiae scattered thickly in the anterior portion of this structure. Sections through the cerebellum and medulla revealed similar but less striking appearances in the white matter of the descending tracts. Section of the hemispheres showed pinkish congestion of the cortical ribbon but violaceous cyanosis was not observed in this structure. Congestion with ready bleeding from cut vessels was seen throughout the white matter of both hemispheres (Fig. 1), and this was more marked in the region of the basal nuclei (Fig. 2).

Morbid histology

Examination of sections from the lungs showed the features of acute confluent bronchopneumonia. The pancreas and heart showed normal post mortem appearances but the adrenal glands displayed congestion of the cortical vessels with small diffuse haemorrhages in the cortico-medullary junctional zone. The liver showed widespread congestion of centrilobular veins with early fatty infiltration of liver cells in the centrilobular /

centrilobular parenchyma.

Inclusion bodies were not observed within the cells in any of the sections examined.

The lesions in the central nervous system were for the most part perivascular in site and in general confined to the white matter. Veins, venules and capillaries were affected. Where the lesions were slight or moderate the veins alone showed characteristic changes, where the lesions were severe the capillaries also were affected. The arteries throughout appeared normal. The meninges did not show severe changes at any level either within the cranium or spinal canal.

Congestion of the veins was a common feature in all areas affected and this was accompanied by varying degrees of perivenous lymphocytic infiltration. The infiltrating cells were everywhere of the same kind within the substance of the brain and polymorphonuclear leucocytes and plasma cells were not observed. In areas with maximum damage, ball and ring haemorrhages were present and here also endothelial swelling of the venules and capillaries with breakdown of the vessel walls was often evident. At such sites the perivascular cellular infiltrate extended into the surrounding brain tissue. Although well developed ring forms of haemorrhage were not common, these lesions did show frequently central areas of clearing which did not reveal a deposit of haemosiderin in appropriately stained sections. In many cases a delicate background of myelinated fibres was present in the central cleared /

cleared area. Demyelination was not seen either in relation to haemorrhages or where vascular necrosis was present even in relation to larger veins. Isolated areas of demyelination unassociated with any vessel were also absent. Small zones of microglial proliferation were found in relation to capillary lesions and in areas where many capillaries were affected there was a generalised increase in the number of microglial nuclei. Small nodules of microglial proliferation were also sometimes to be seen apparently unrelated to vascular lesions.

Sections from all levels of the spinal cord were examined and the appearances were generally within normal limits. Slight venous congestion was present in the meninges at most levels but in the lower thoracic region a small quantity of proteinous exudate was thinly spread in the subarachnoid space. A sparse cellular infiltrate of lymphocytes was present here. At this level also, venous congestion was present within the grey matter of both anterior and posterior horns (Fig. 3), and in the left posterior horn small haemorrhages had occurred (Fig. 4). The adjacent white matter on either side of the horn showed congestion and a few tiny haemorrhages.

The meninges of the pons and medulla displayed moderate venous congestion with slight proteinous exudate in the subarachnoid space. Here also was a sparse cellular infiltrate composed for the most part of lymphocytes together with a few macrophages and an occasional polymorph. Within the white matter of the medulla congestion was evident at all levels affecting /

affecting veins of all sizes. A few small veins showed endothelial swelling and in some instances vascular necrosis had permitted the escape of erythrocytes into the perivascular space. The veins in the nuclear masses were congested but otherwise little affected. Within the pons, similar, but more severe venous congestion was present. Here a proteinous coagulum was often deposited within the veins and in some instances was present also in the Virchow Robin space. Cellular cuffing was more marked and endothelial swelling and vascular necrosis were more frequent. Foci of microglial proliferation were present in the white matter (Figs. 5 and 6).

The meninges of the cerebellum displayed only moderate venous congestion. The veins associated with the dentate nuclei were congested and a proteinous coagulum was frequently present within the lumen. Endothelial swelling and slight perivenous cellular infiltrate were also evident. Venous and capillary congestion of some degree and marked venous cellular cuffing were features of the white matter in both cerebellar hemispheres. Small foci of microglial proliferation were present about scattered capillary lesions. In the left cerebellar hemisphere small ball haemorrhages were infrequently found close to the granulosal cell layer.

Sections from the brain stem did not show any striking features although generalised congestion and slight cuffing of many veins was present.

Material from the basal ganglia and third ventricle showed the presence of occasional small ball haemorrhages in the /

the immediate sub-ependymal areas but these lesions were not numerous and venous congestion and cuffing were slight in the nuclear masses.

The meninges of the cerebral hemispheres generally were the seat of moderate venous congestion. These changes were more severe over the right frontal lobe where proteinous exudate and slight haemorrhage had occurred in the subarachnoid space. Within the cerebral hemispheres material from the occipital, parietal and temporal lobes of both sides showed varying degrees of moderate venous congestion in the cortical ribbon. Where the lesions in the underlying white matter were most severe, capillary congestion also was present in the cortex. Ball haemorrhages showing partial central clearing were present in several areas in the white matter of the right cerebral hemisphere but these lesions were not associated with local demyelination. (Figs. 7 and 8). On the same side also examples of severe venous congestion and cellular cuffing were not infrequently to be seen (Figs. 9 and 10).

The most severe lesions encountered were present in the corpus callosum and in the corona radiata of both sides. Numerous ball and ring haemorrhagic forms were thickly scattered in many areas examined and associated with these also were numerous examples of vascular necrosis, cellular infiltration and microglial proliferation. Endothelial swelling was a common feature in veins and capillaries and cuffing was often very marked (Figs. 11, 12 and 13).

Inclusion bodies were not observed either in nerve cells or glial cells in any of the sections examined.

CASE 7

FIGURES 1 - 14

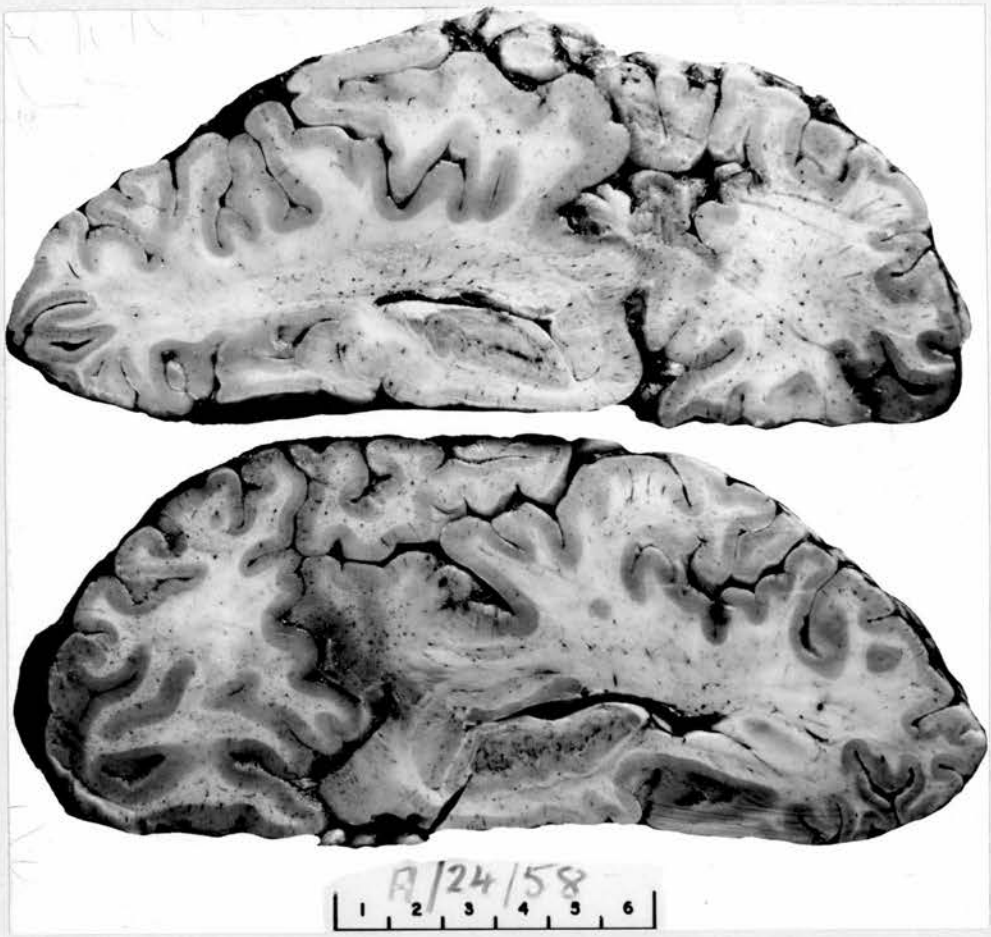

Fig. (1) Left (above) and right cerebral hemispheres. Punctate haemorrhagic lesions are scattered diffusely in the white matter on both sides of the cerebrum.

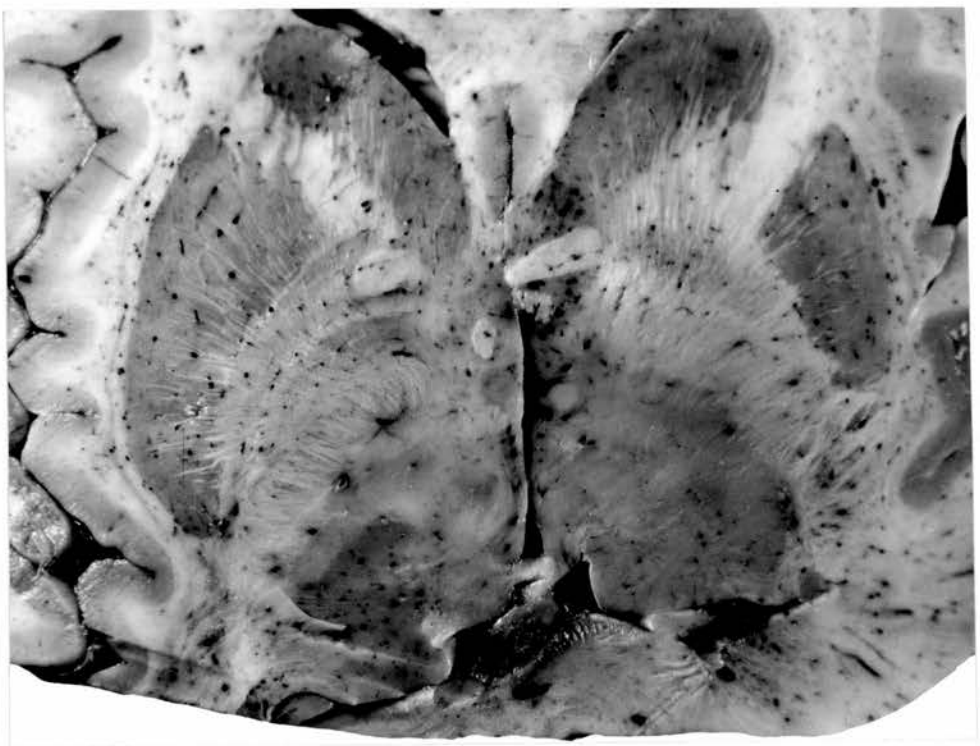

Fig. (2) Basal nuclei and internal capsules.
Punctate haemorrhagic lesions are more numerous in the white matter.

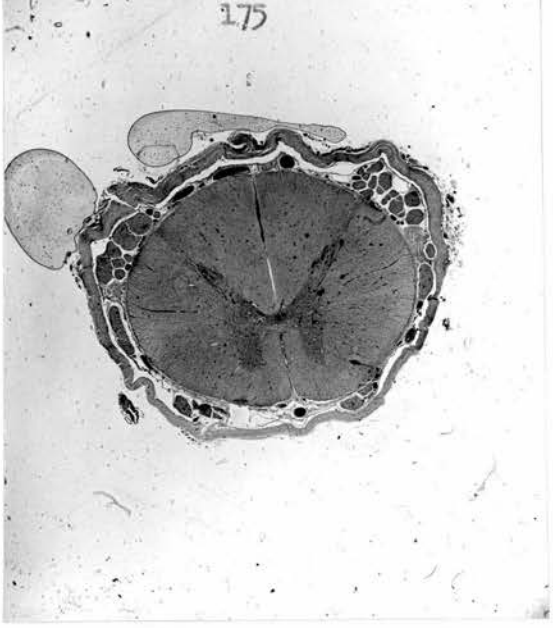

Fig. (3) Transverse section of the spinal cord; lower thoracic level.
Congestion and small haemorrhages are present in the grey matter of the left posterior horn.
Small haemorrhages are also evident in the adjacent white matter.
Eosin, phloxine and tartrazine; (X5).

Fig. (4) Detail of Fig. (3).
Congestion and a single small haemorrhage are evident in the grey matter of the left posterior horn.
Eosin, phloxine and tartrazine; (X125).

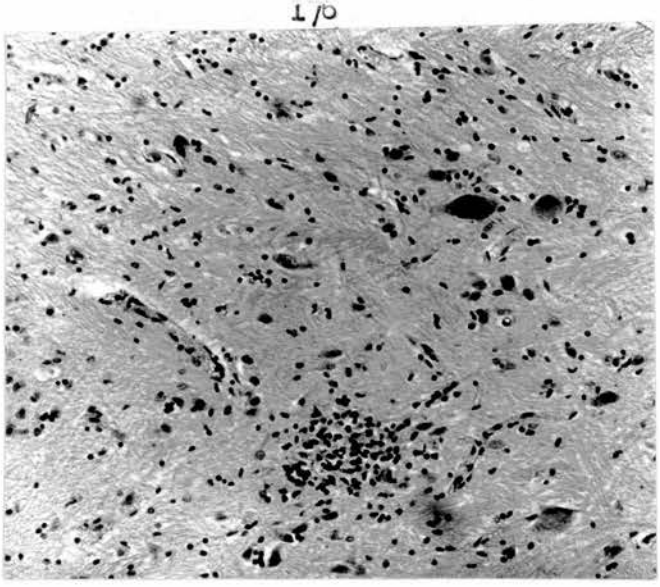

Fig. (5) Left side of pons.
A nodule of microglial proliferation is present.
Haemalum and eosin; (X140).

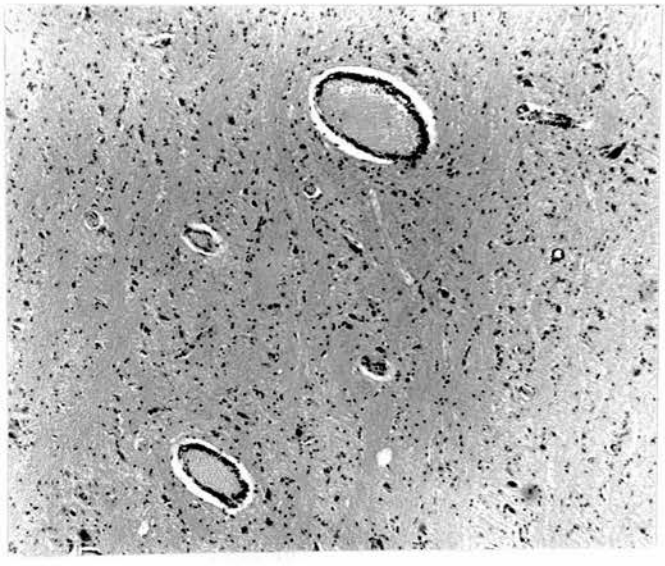

Fig. (6) Left side of pons.
Venous congestion is evident. The vessels are surrounded by a sparse cuff of lymphocytes.
Haemalum and eosin; (X65).

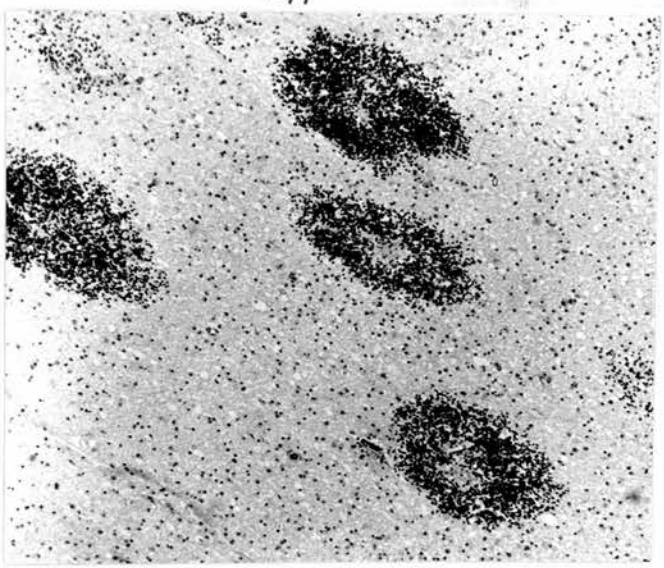

Fig. (7) White matter of the right cerebral hemisphere. Ball haemorrhages show partial central clearing. Eosin, phloxine and tartrazine; (X65).

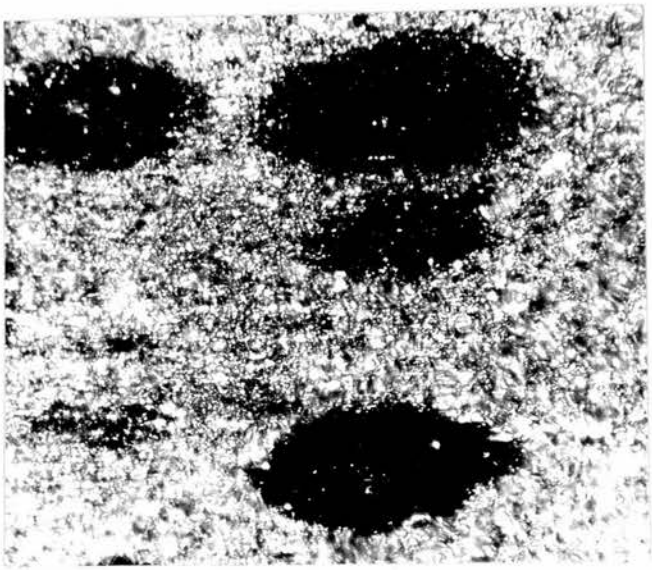

Fig. (8) White matter of the right cerebral hemisphere. Ball haemorrhages are unassociated with local demyelination. Loyez; (X65).

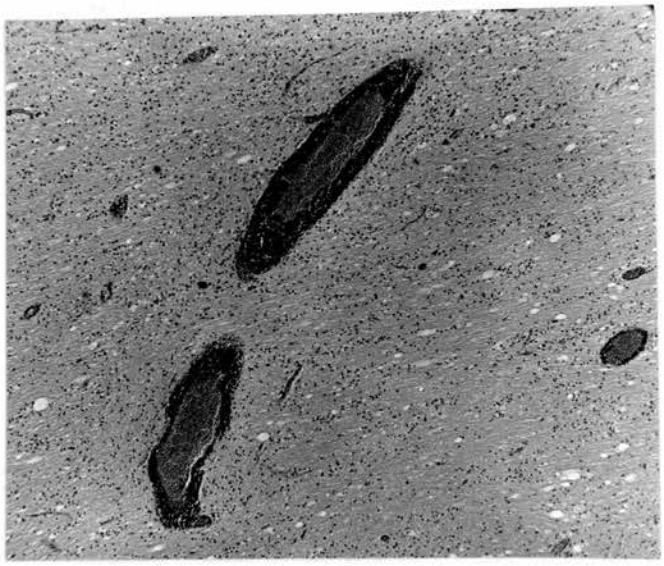

Fig. (9) White matter of the right cerebral hemisphere. Congested veins show a severe degree of lymphocytic cuffing. The cellular infiltrate is limited to the Virchow-Robin spaces.
Haemalum and eosin; (X40).

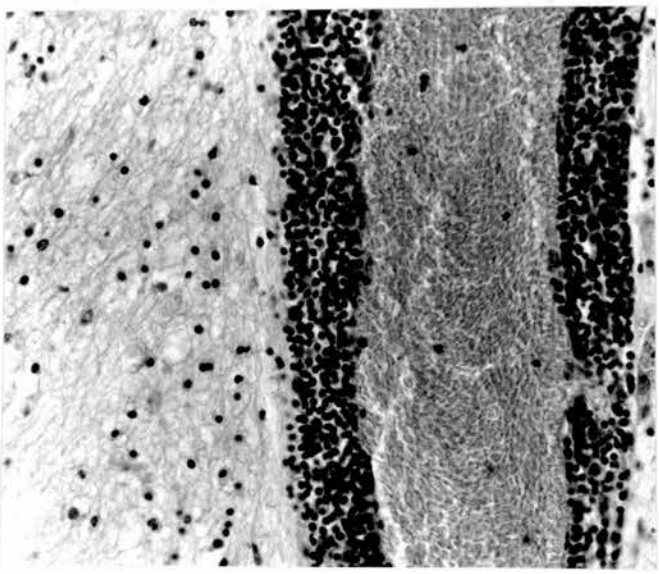

Fig. (10) Detail of Fig. (9).
Detail of perivenous lymphocytic infiltrate.
Haemalum and eosin; (X225).

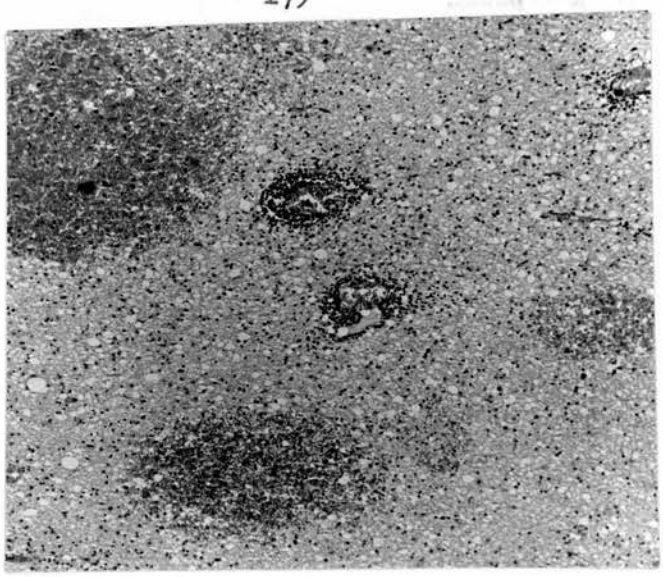

Fig. (11) Left side of splenium.
Haemorrhages and venous congestion are evident in the white matter. Two small veins show lymphocytic cuffing and microglial proliferation is apparent in the zone about these vessels.
Eosin, phloxine and tartrazine; (X65).

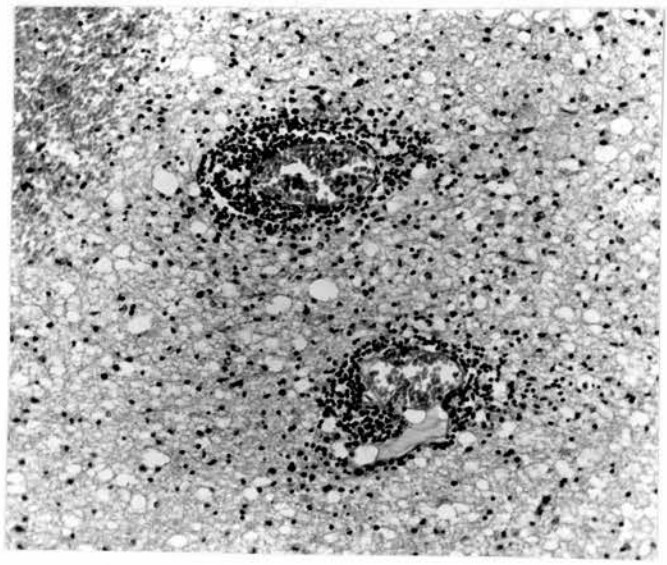

Fig.(12) Left side of splenium.
Detail of Fig. (11).
Eosin, phlozine and tartrazine; (X130).

Fig. (13) Corpus callosum.
Large ball haemorrhages are present showing slight central clearing. Microglial proliferation is apparent about congested capillaries.
Eosin, phloxine and tartrazine; (X65).

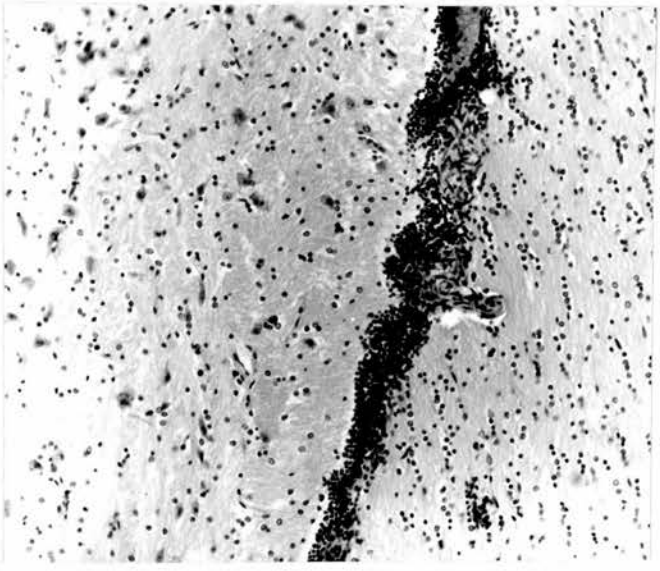

Fig. (14) Rabbit brain. Death on ninth day after intracerebral inoculation with virus suspension from Case (7).
Perivenous lymphocytic cuffing is evident at the junction of the cortex and medulla.
Haemalum and eosin; (X125).

CASE 1. (Second admission).

Sex: Female.

Age: 20 years.

Complaint

26.1.58. The patient complained of a violent headache and retired to bed. The headache persisted and on the following day was accompanied by a right sided facial paresis; the patient's condition continued to deteriorate and on 31.1.58 a right-sided hemiparesis developed.

Previous history

The patient had not consulted her medical attendant since her discharge from hospital on 8.8.57. A few days before the onset of headache on 26.1.58 she had complained of a severe cold with sore throat and cough but she did not have any other complaints. The patient had begun to menstruate on 27.1.58, and on this day her doctor had initiated a course of sulphonamide therapy.

State on admission

1.2.58. The patient was menstruating at the time of admission. She was semiconscious but unable to speak and responded to painful stimuli by movement of the left arm and left leg. Examination of the cardiovascular system did not give evidence of organic disease. The blood pressure was 130/70 mm.Hg. Dullness was elicited over the right lung apex and the patient had a productive cough. Examination of the nervous /

nervous system disclosed no signs of raised intra-cranial pressure. Hemiparesis of the right side was present. The Right plantar response was extensor and Kernig's sign was positive. Marked nuchal rigidity was evident.

Investigations

Cerebrospinal fluid:-

Pressure (patient recumbent)	Cells
280 mm/water	750/cu.mm. Polymorphs.

Blood:-

W.B.Cs. 10,000/cu.mm.

A provisional diagnosis of cerebral abscess was made and the patient was transferred to a neurosurgical unit.

2.2.58. On admission after transfer the patient's condition was substantially unchanged. Radiographic examination of the lung fields showed appearances consistent with early consolidation in the right middle lobe. The skull did not show any abnormality on X-ray examination. A ventriculogram showed displacement of ventricular outlines to the right and these appearances suggested the presence of an expanding lesion in the left parietal lobe.

2.2.58. The patient died after these preliminary studies had been made.

Necropsy

The body was that of a young woman of good nutrition and normal development. There were no superficial features of note and apart from the findings of oedema, congestion and early consolidation /

consolidation in the middle and lower lobes of the right lung, the positive findings were confined to the central nervous system.

The brain was of average size. Superficial congestion was marked over both hemispheres. The left hemisphere was slightly larger than the right and the enlargement was uniform throughout its substance. Section disclosed widespread and intense congestion throughout almost all the white matter in both cerebral hemispheres, mid brain, cerebellum, pons and upper medulla. In the cerebral hemispheres the congested areas were scattered with leashes of tiny haemorrhages; these were more prominent in the subcortical region. Lesions were more profuse on the left side (Figs. 1 and 2) so that the substance of the left hemisphere bulged into and partially occupied the lumen of the left lateral ventricle. Similar appearances were seen in the white matter of the cerebellar hemispheres (Fig. 3) but the lesions here did not display the same asymmetry of distribution seen in the cerebrum. The cortex throughout appeared macroscopically to be spared.

Morbid histology

The lesions in the central nervous system were in large measure confined to vessels and their immediate surroundings. Small veins, venules and capillaries were all affected and showed all degrees of damage from endothelial swelling to complete necrosis. Widespread infiltration of polymorphonuclear leucocytes /

leucocytes was observed in the leptomeninges and in the Virchow Robin spaces about the affected vessels within the brain itself. In the less severely affected regions some cells were densely packed about vessels, forming a characteristic cuff. In other areas, where damage was more severe, vascular necrosis had occurred, particularly in small venules and capillaries, and polymorphs were seen infiltrating widely between axons. Fibrinous exudate was seen in some instances in the walls of affected vessels, in the Virchow Robin spaces and spreading between adjacent structures. Diffuse haemorrhages were present in many areas; well rounded ball forms were seen only in a few places. Some of these lesions showed slight central clearing but established ring forms were not observed. Perivascular demyelination was evident in a few areas but in general this was not a prominent feature. Areas of demyelination unassociated with vessels were not seen. The white matter throughout the brain was most severely affected and the cortex showed lesions of minor severity only in those areas where the damage in the adjacent white matter was most severe and most widespread. The leptomeninges were the seat of similar vascular lesions with proteinous exudate and polymorph cellular infiltrate but these were always less severe than those in the substance of the brain.

The appearances at the level of the lower medulla were within normal limits. At the level of the lower end of the fourth /

fourth ventricle venous congestion and perivascular cuffing were evident (Figs. 4 and 5). Perforating vessels at this level showed dense cuffing with polymorphs (Fig. 6). The white matter of the cerebellar hemispheres displayed widespread and severe lesions. Congestion, endothelial swelling, vascular necrosis with extravasation of erythrocytes were all evident and wide migration of polymorphs was apparent in some areas (Figs. 7 and 8). The lesions in the left cerebellar hemisphere were more severe than those in the right. Within the pons the vascular lesions were similar in all details but more severe and more widespread. Fibrinous exudate and remarkably diffuse polymorph infiltration were conspicuous in many areas (Fig. 9). The leptomeningeal lesions were also marked at this level. Up to this level the vascular changes were not associated with demyelination about the affected areas.

Within the cerebral hemispheres the lesions were scattered thickly in all parts of the white matter. Lesions were more profuse and severe in the left hemisphere than in the right. In the white matter adjoining the central gyrus of the left frontal lobe the vascular lesions were very severe and necrosis of small vessels was conspicuous (Figs. 10 and 11). Similar changes were apparent in the white matter of the left parietal lobe (Fig. 13). The cortex at this site also showed venous cuffing and endothelial swelling. The leptomeninges were, however, less severely affected at this level than at the pons. In this area also early perivascular demyelination

was evident in some instances. In corresponding sections from the right hemisphere venous congestion was prominent in the white matter and a few cortical veins showed endothelial swelling but cuffing was not marked. The leptomeninges on this side were relatively normal. The corpus callosum was the seat of very severe lesions which included the smallest venules and capillaries. Widespread vascular necrosis with fibrinous exudate, migration of polymorphs, ball haemorrhages and perivascular demyelination were all prominent here, together with generalised proliferation of microglial cells (Fig. 12).

Lesions in the temporal lobes on either side were less severe and were of comparable degree on either side. Early perivascular demyelination and microglial proliferation were evident in the white matter in these sites.

CASE 1

FIGURES 1 - 13

Fig. (1) Left cerebral hemisphere.
The distribution of punctate haemorrhagic lesions in the white matter is apparent.

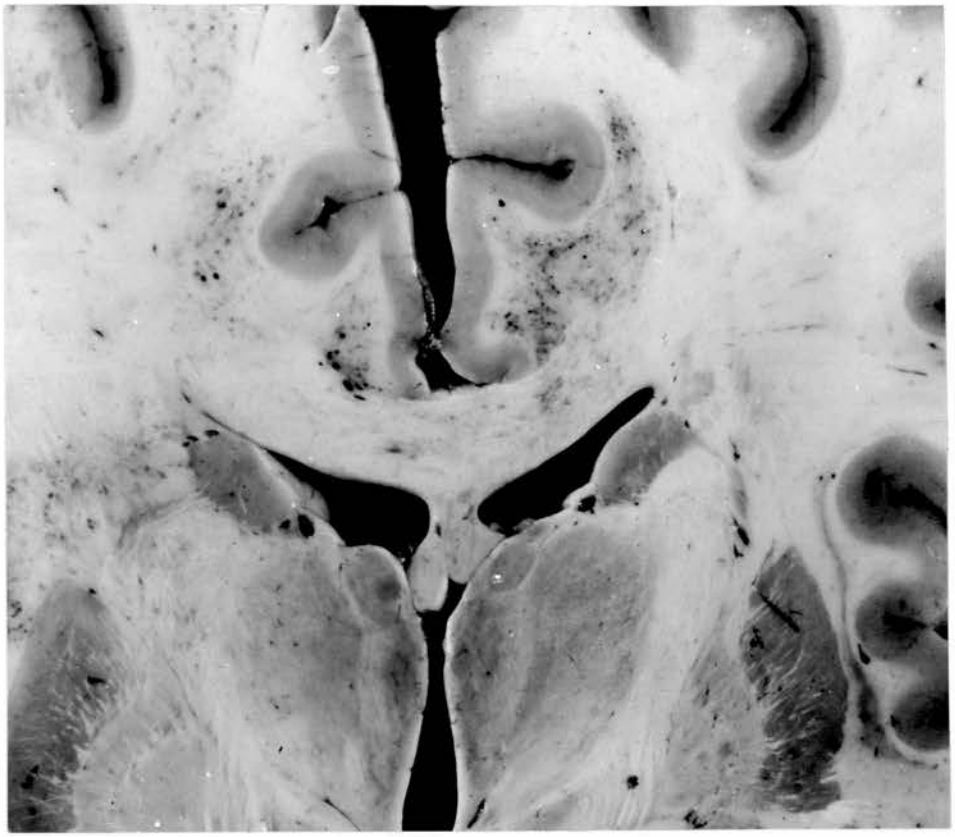

Fig. (2) Cerebrum.
Punctate haemorrhagic lesions are distributed thickly about the corpus callosum.

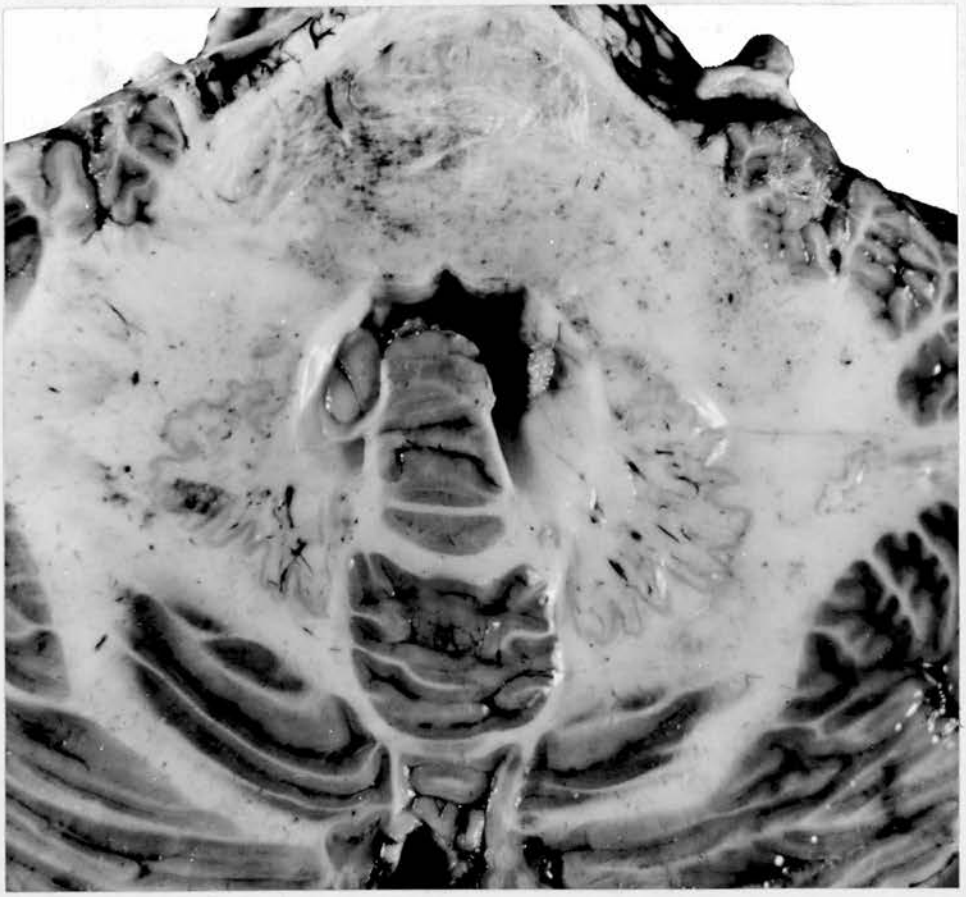

Fig. (3) Cerebellum.
Punctate haemorrhagic lesions are present in the white matter of both cerebellar hemispheres.

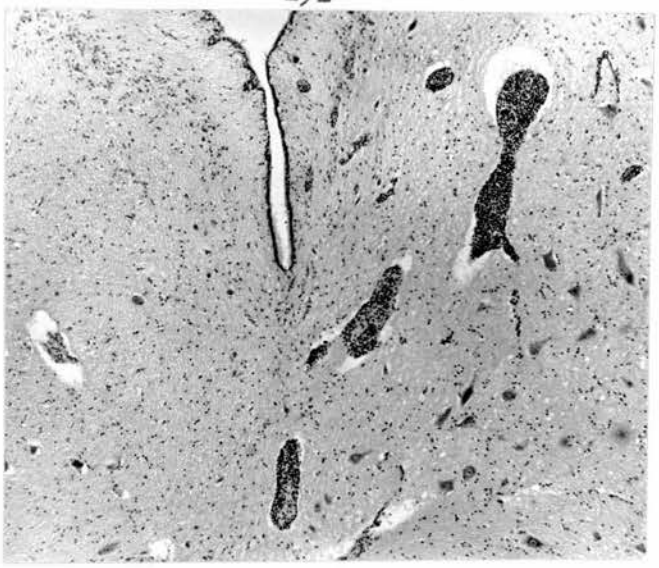

Fig. (4) Floor of the fourth ventricle.
Severely congested veins display dense cuffs of polymorphonuclear leucocytes.
Haemalum and eosin; (X50).

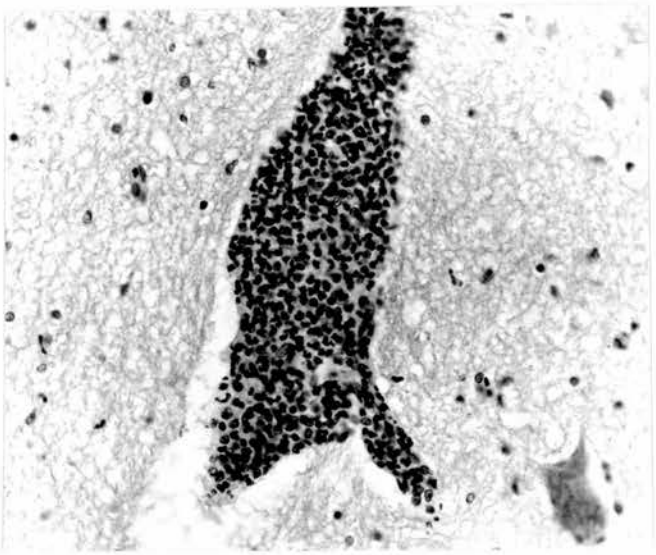

Fig. (5) Floor of the fourth ventricle.
Detail from Fig. (4).
Haemalum and eosin; (X225).

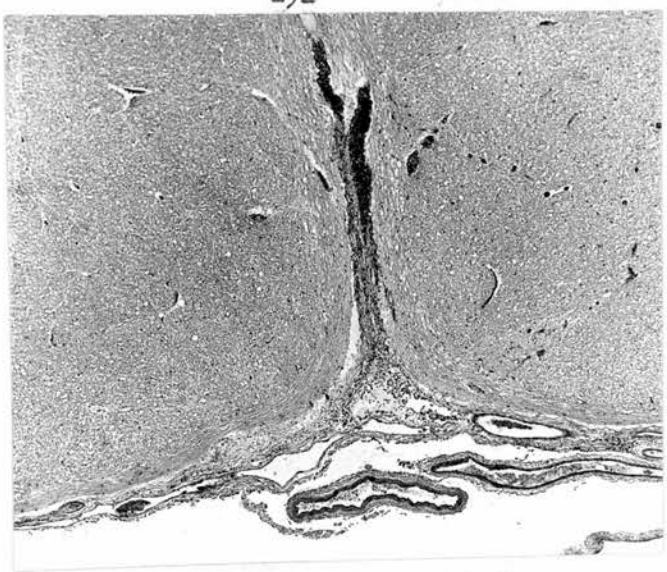

Fig. (6) Anterior surface of the brain stem at same level as Fig. (4).
Perforating vessels bear dense cuffs of polymorphonuclear leucocytes.
Haemalum and eosin; (X35).

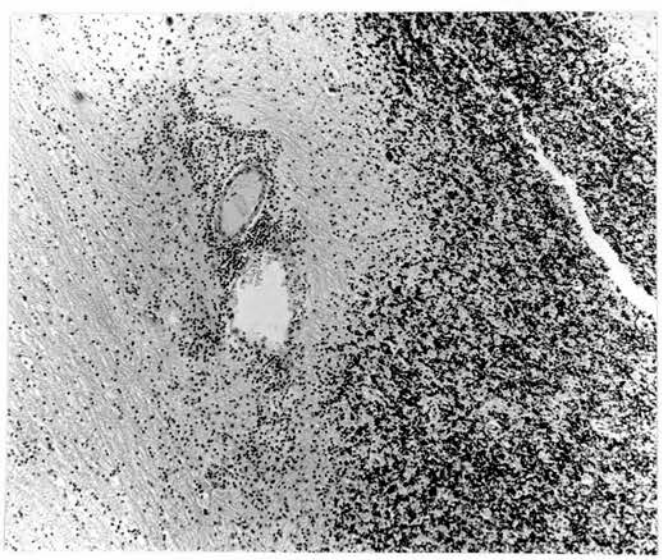

Fig. (7) White matter of the left cerebellar hemisphere.
Diffuse perivenous infiltration with polymorphonuclear leucocytes is present.
One vein shows a severe degree of vascular necrosis.
Haemalum and eosin; (X60).

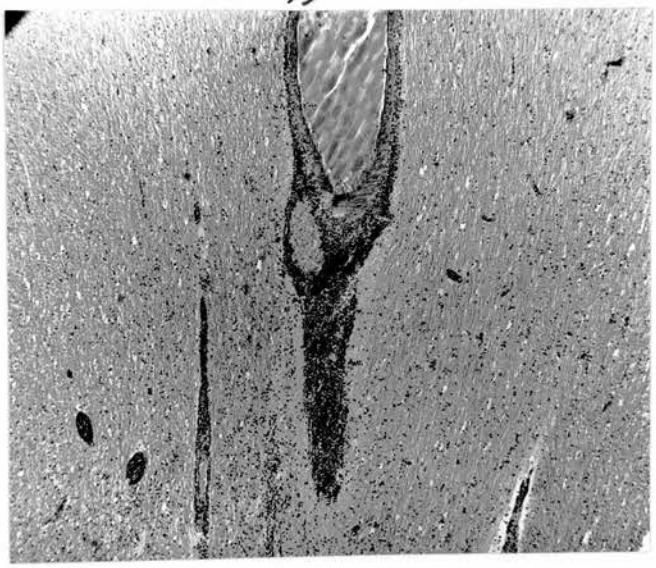

Fig. (8) White matter of the right cerebellar hemisphere. A large congested vein is densely infiltrated by polymorphonuclear leucocytes. Migration of these cells between adjacent fibre bundles is apparent. Haemalum and eosin; (X35).

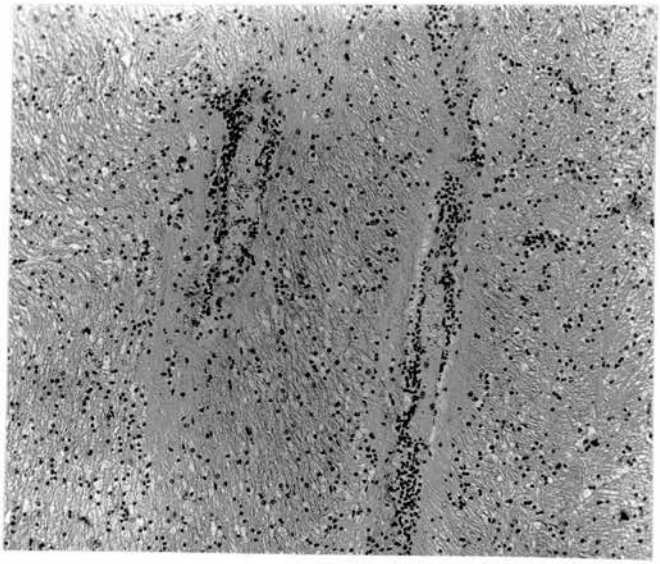

Fig. (9) Pons.
Perivascular cuffing with polymorphonuclear leuco-:cytes is present. The vascular lesions are more severe and endothelial swelling and partial disintegration of the vessel walls is apparent. Haemalum and eosin; (X80).

Fig. (10) Cerebrum; white matter of the left frontal lobe. Severe lesions are evident in venules and capillaries with endothelial swelling and rupture. Perivascular proteinous exudate, irregular areas of haemorrhage and widespread infiltration by polymorphonuclear leucocytes are present. Eosin phloxine and tartrazine; (X35).

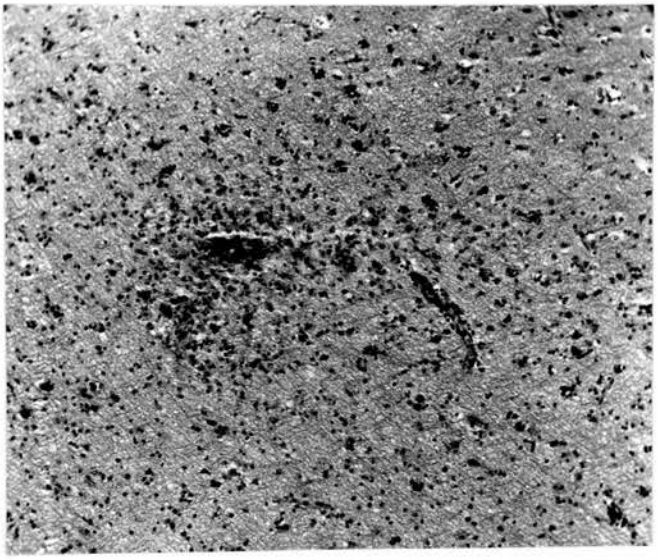

Fig. (11) Cerebrum; white matter of the left frontal lobe. Necrosis of a venule with widespread polymorphonuclear leucocytic infiltration is apparent. Proliferation of microglial nuclei is evident about the vascular lesion. Haemalum and eosin; (X80).

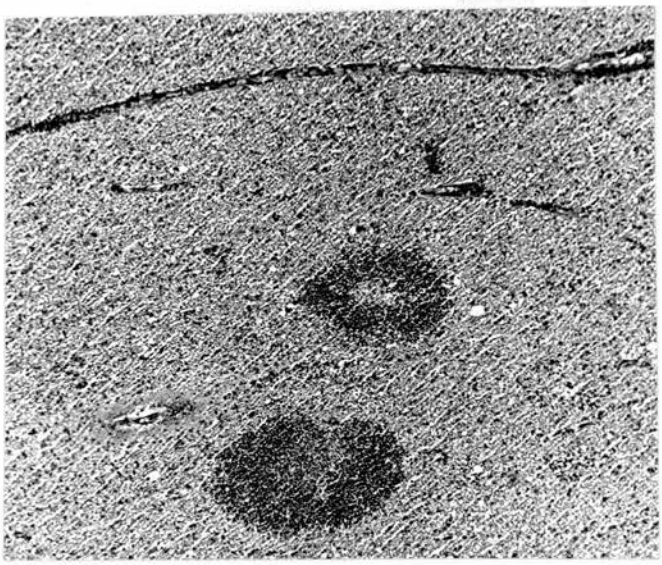

Fig. (12) Corpus callosum.
Ball and ring haemorrhages. The small vessel shows a cuff of polymorphonuclear leucocytes.
Haemalum and eosin; (X55).

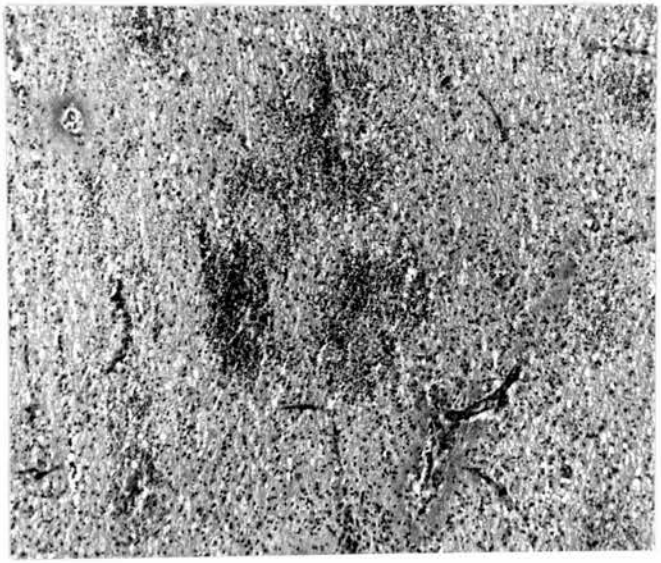

Fig. (13) Cerebrum; white matter of the left parietal lobe.
Diffuse haemorrhages, capillary congestion and necrosis are present. A general increase in the number of microglial nuclei is apparent.
Eosin phloxine and tartrazine; (X65).

CASE HISTORIES

GREENOCK GROUP B CASES 8 - 10

CASE 8

Sex: Female

Age: 5 years

Complaint

5.3.59. The patient was found unconscious in the morning with generalised muscular twitching.

Previous history

The patient, the third of a family of four children was born after a normal pregnancy and confinement. The patient had had measles in infancy and had made a normal recovery from this disease. She had been inoculated against poliomyelitis in December 1958.

On 2.3.59 the child developed what was thought to be an attack of influenza and this condition persisted until the onset of the symptoms described on 5.3.59.

State on admission

5.3.59. The patient was a fairly well nourished small girl deeply comatose and displaying spastic paralysis of all limbs. Apart from scattered rhonchi heard in both lung fields, the positive findings on examination were confined to the nervous system.

Neck stiffness was not apparent and Kernig's sign was negative. Both upper and lower limbs were spastic. The legs were held in position of extreme spastic extension. The arms were spastic and slightly flexed at shoulder and elbow /

elbow. The hands were held in the main en griffe position. Tendon reflexes were present and equal. The plantar response was extensor on the right side but flexor on the left. A slow lateral nystagmus was present with a left internal strabismus. The pupils were equal but reacted only very sluggishly to light. Examination of the fundi did not reveal evidence of papilloedema.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
5.3.59.	10/cu.mm.	760 mg%	360 mg%	88 mg%

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.	E.S.R.
5.3.59.	15.5 gms%	45	34%	8,100/cu.mm.	4 mm 1 hour

Virology:-

6.3.59. Type A influenza virus isolated from lung.

Medulla) No virus isolated by egg inoculation
Pons) (chorioallantoic and amniotic routes).

9.3.59. No virus isolated from medulla and pons by inoculation of mice intracerebrally and He La tissue cultures.

9.3.59. Pons: Intraperitoneal inoculation of suckling mice: No virus isolated.

9.3.59. R. cortex, L. cortex and Lumbar cord: No virus isolated by inoculation of eggs (chorioallantoic) or tissue cultures.

Progress

The child showed no improvement and her condition steadily /

steadily deteriorated, with a pre-terminal pyrexia of 104°. She died eight hours after admission to hospital. Necropsy was performed within one hour of death.

Necropsy (one hour after death)

The body was that of a female child of fair nutrition. The legs were held in extension and the feet in marked plantar flexion. The upper limbs were slightly flexed at the elbows.

With the exception of the central nervous system the only positive findings were in both lungs which showed bilateral areas of haemorrhagic consolidation in the lower lobes. The other organs of the thorax, abdomen and pelvis were healthy.

The scalp and skull were healthy. The dura was under increased tension and, on incision, the brain bulged freely through this membrane. The surfaces of both cerebral hemispheres were symmetrical and showed moderate superficial congestion. There was no excess of cerebrospinal fluid anywhere in the subarachnoid space nor was any free blood present.

Section of the brain at the level of the upper margin of the pons showed the presence of an intense haemorrhagic lesion in the substance of the brain at this level. The nervous tissue was softened and densely infiltrated by haemorrhage. This area of haemorrhage which was most evident about the centre of the brain stem was surrounded /

surrounded by a thin rim of softened white matter. The lesion extended with ill defined margin up into the mid brain and down into the pons with some indefinite extension into the superior cerebellar peduncle. Section of the medulla showed, however, that the haemorrhagic lesion did not extend to this level and only moderate congestion was evident here. The upward extension of the lesion similarly was limited to the mid brain and sections above this level again showed only moderate congestion.

The most severely affected portion of the pons was removed with suitable sterile precautions and submitted for virological examination. Both Gasserian ganglia were identified and half of each structure was also sent for virological examination together with specimens from the medulla and both cerebral hemispheres and from the most severely affected portions of both lungs.

Examination of the base of the skull did not reveal any lesions in the bony structure or in its associated structures. Both middle ears were dissected and no gross evidence of infection was found.

Morbid histology

Sections from the lungs showed diffuse haemorrhagic bronchopneumonia widespread in both lungs. Histological examination of other organs than the brain did not show any features of disease. In particular, histological appearances were normal in those portions of both Gasserian ganglia which had /

had not been submitted for virological examination.

Brain: The lesions in the pons were conspicuously those of multiple small haemorrhages arising from severely damaged venules and capillaries indifferently dispersed between nuclei and white matter. The haemorrhages did not present any particular form and no examples either of ring or ball forms were anywhere evident. The shape of the haemorrhagic lesions appeared to be determined by the orientation of adjacent nervous bundles so that the blood had penetrated along the lines of least resistance (Fig. 5). In many areas these extravasations were becoming confluent. Recognisable vascular architecture was often not to be found within the haemorrhagic areas. The Virchow-Robin spaces about some larger veins sometimes contained small numbers of erythrocytes and a few small veins were cuffed with round cells and polymorphs in small numbers, but these lesions were neither frequent nor severe (Figs. 5 and 6). The ventral portions of the brain stem were most severely affected but similar changes of less severity were present also in dorsal fields. Generalised venous congestion with dilatation of the Virchow-Robin spaces was marked at this level.

In the basal ganglia a few small veins were moderately congested and these occasionally were associated with small extravasations of erythrocytes in the Virchow-Robin spaces. Minor degrees of cuffing of some small veins were seen in a few instances and these changes were approximately /

approximately of the same slight to moderate frequency on both sides.

The only features of note in sections prepared from both cerebral hemispheres were of similar venous and perivenous lesions confined to the Virchow-Robin spaces in the white matter. These were of slight or moderate severity but were relatively infrequent in the fields examined. In these veins where cuffing was apparent rather more polymorphs were observed than had been seen elsewhere. Haemorrhagic lesions with extravasations of blood between the nervous bundles were not found anywhere other than in the pons. The cortex appeared normal in all fields.

Within the white matter of both cerebellar hemispheres several small veins were moderately congested and these occasionally were associated with small extravasations of erythrocytes in the Virchow-Robin spaces. In both cerebellar hemispheres the cortex appeared unaffected.

Sections from the medulla and spinal cord showed only normal features.

The changes in the leptomeninges were confined to a moderate degree of venous congestion in the region of the pons and medulla. Over the ventral aspect of the pons minor extravasations of erythrocytes were observed.

CASE 8

FIGURES 1 - 6

CASE 8

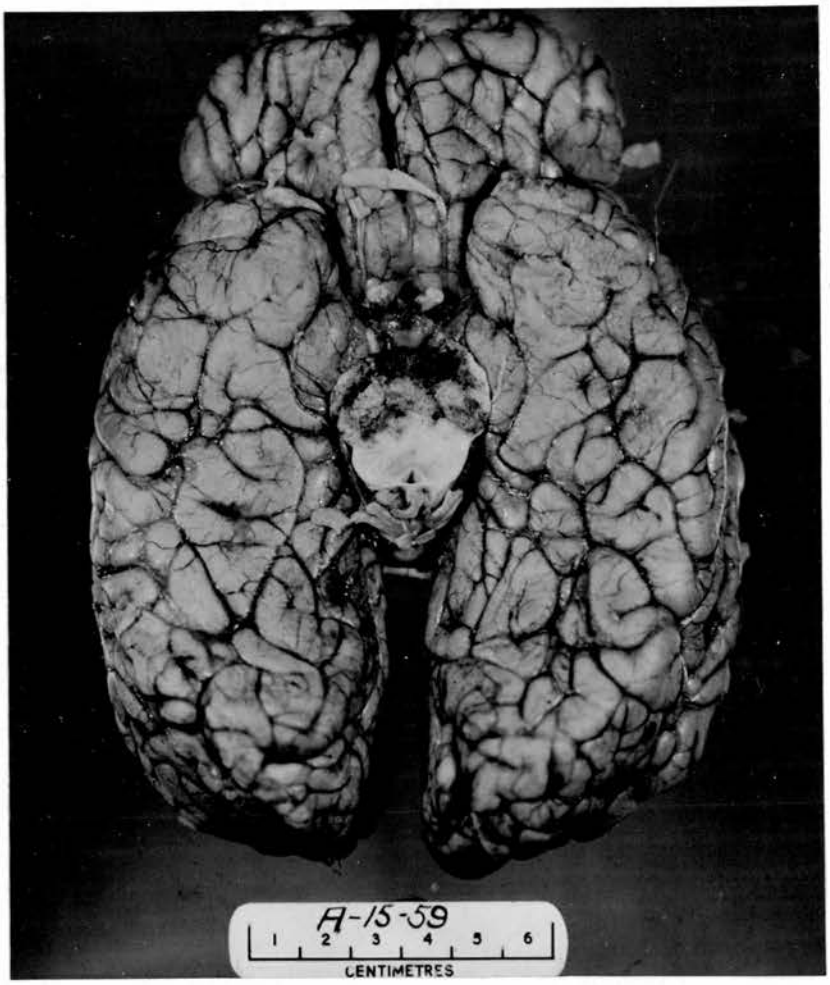

Fig. (1). Section at upper level of pons.

Haemorrhagic lesions are numerous in the ventral aspect of the brain stem.

CASE 8

Fig. (2). Cerebral hemispheres.

The appearances at this level are those only of moderate congestion most evident in the white matter.

CASE 8

Fig. (3). Cerebral hemispheres.

The appearances are within normal limits.

CASE 8

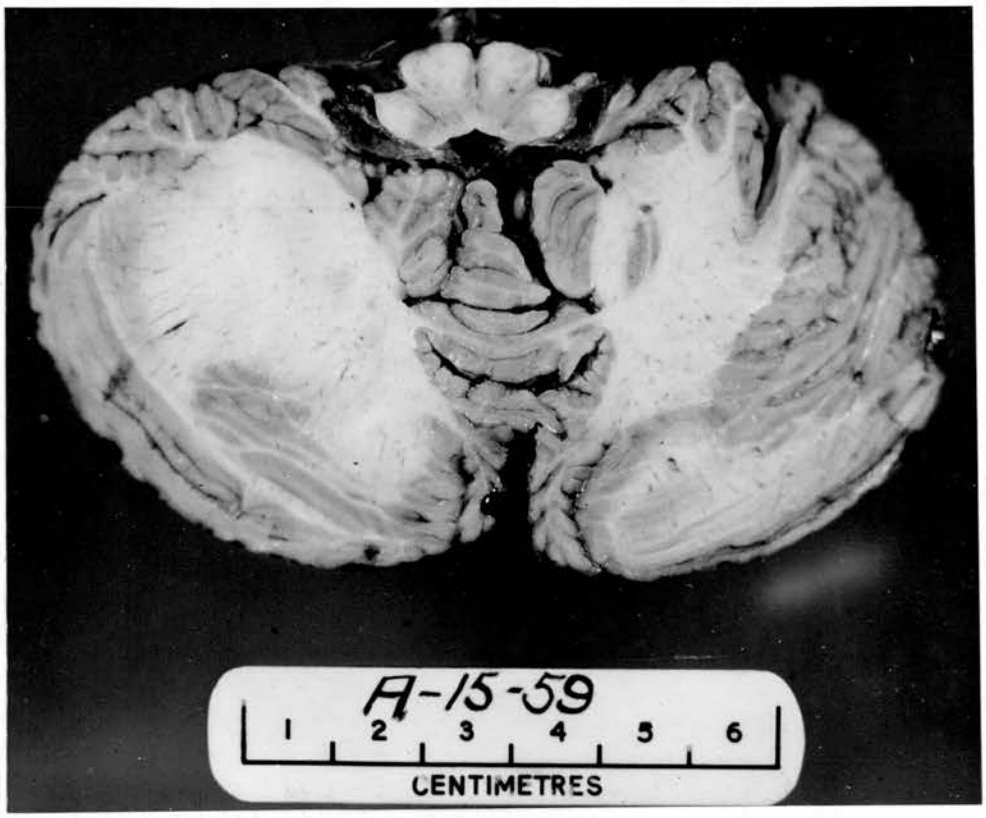

Fig. (4). Medulla and cerebellar hemispheres.

Slight to moderate congestion is apparent in the white matter.

CASE 8

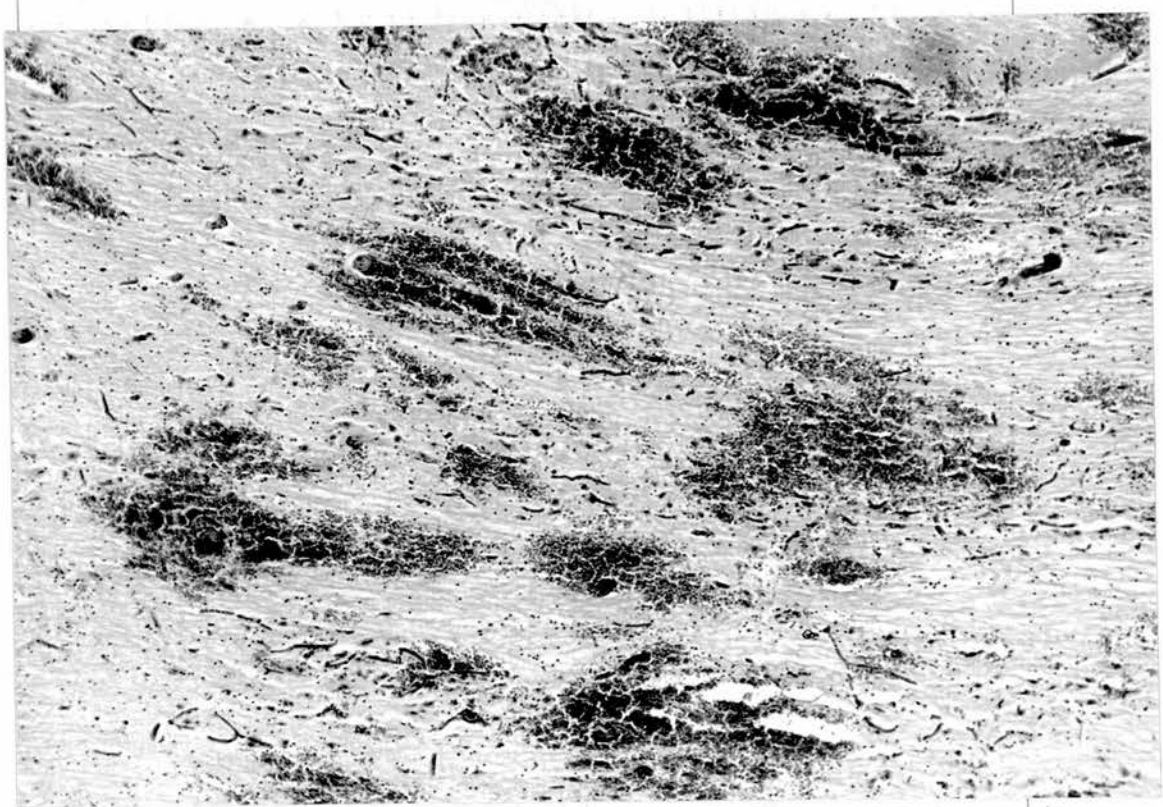

Fig. (5). Pons.

Scattered irregular haemorrhages are present both in the nuclear masses and in the white matter. (Haemalum and eosin X 65).

CASE 8

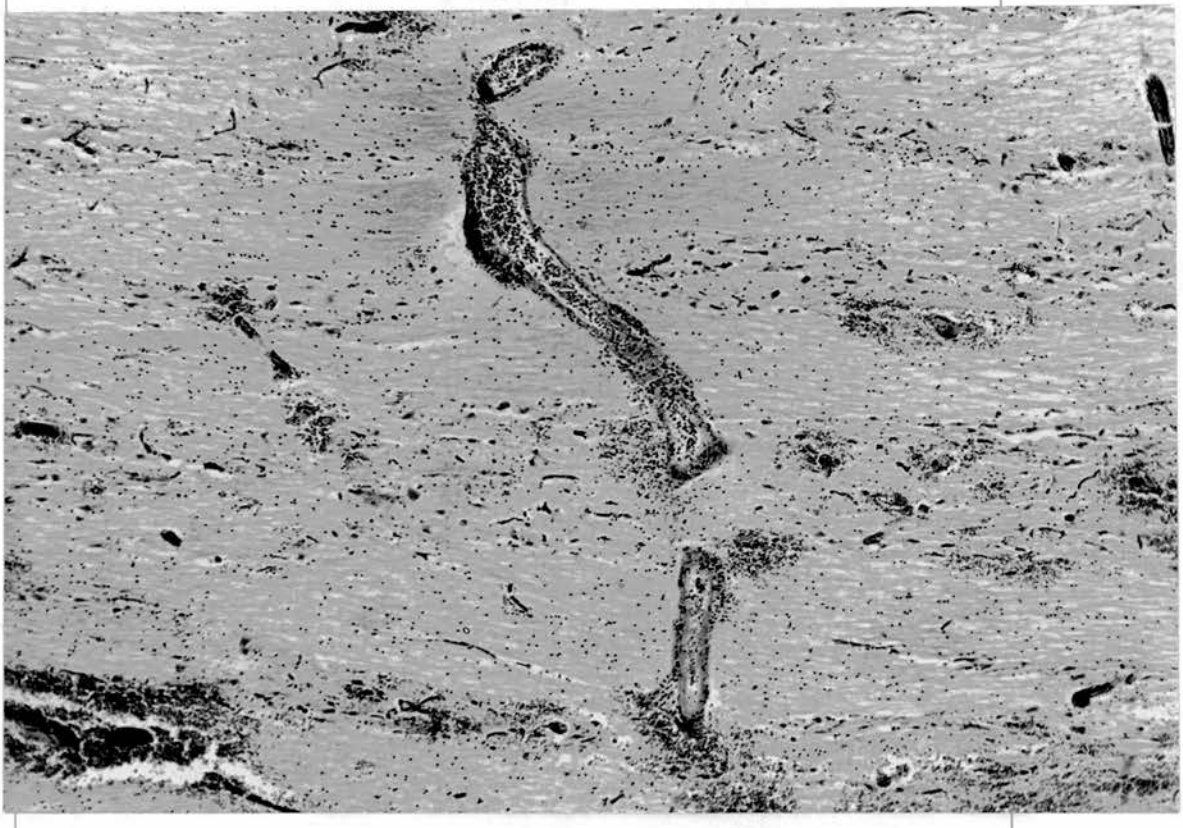

Fig. (6). Pons.

Endothelial swelling, haemorrhage and cuffing of several venules and of a larger vein by round cells and polymorphs.

CASE 9

Sex: Male

Age: 4½ years

Complaint

The patient became ill on 13.4.59 with anorexia, sweating and irritability and he remained in this condition for a week before admission to hospital. One hour before admission he developed a prolonged convulsive seizure.

Previous history

The patient was born after a normal pregnancy and confinement and no significant features were elicited in the family or social history. In early infancy the patient had been healthy but eight weeks before admission to hospital he had had an attack of measles from which he had made, apparently, a normal recovery. Two weeks before admission to hospital his parents had observed that the patient displayed intermittent twitching of his left arm and this disorder recurred from time to time until the onset of the present illness on 13.4.59.

State on admission

20.4.59. Temperature 97.4 °F; pulse 160/min; respiration 40/min. The patient was an acutely ill child of good nutrition. He was in coma and his face was cyanosed. Twitching was observed on the left side of the face, left arm and /

and left leg. Despite the administration of intramuscular phenobarbitone, the twitching did not cease until six hours after admission. The pupils were equal but did not react to light. Congestion was evident in both ear drums.

Examination of other systems gave only normal findings.

Investigations

Cerebrospinal fluid:-

	Cells	Chlorides	Protein	Sugar
20.4.59.	2/cu.mm.	-	40 mg%	-
21.4.59.	2/cu.mm.	750 mg%	20 mg%	110 mg%
22.4.59.	2/cu.mm.	740 mg%	20 mg%	96 mg%
23.4.59.	4/cu.mm.	720 mg%	30 mg%	96 mg%

Blood:-

	Hb.	P.C.V.	M.C.H.C.	W.B.C.
21.4.59.	13.2 gms%	41	32%	8,000/cu.mm.

Polymorphs	Lymphocytes	Monocytes	Film
66%	30%	4%	No gross abnormality

Bacteriology:-

21.4.59. Rectal swab : No intestinal pathogens isolated.

21.4.59. Throat swab : No growth obtained.

21.4.59. Post nasal swab : No significant growth obtained.

Progress

21.4.59. The convulsive seizures present on admission had ceased but the patient remained comatose. Occasional /

Occasional jerky movements of the head, right arm and right leg were observed. Nuchal rigidity was not present. A flaccid left sided hemiplegia was evident with an absent knee reflex on the affected side.

23.4.59. The patient had been free of convulsive seizures since 21.4.59, but the coma and hemiplegia persisted. In view of the possibility of a space occupying lesion in the central nervous system the patient was transferred on this day to a neurosurgical unit for investigation.

State on admission to Neurosurgical unit

24.4.59. The patient although unresponsive to the spoken word was roused easily by tactile stimuli and cried readily. Flaccid paralysis of the left arm and left leg was apparent but movements were normal in the limbs of the right side. The pupils were large and did not react to light, the margins of the fundi were blurred. The reflexes were elicited but were diminished on the left side. The left plantar response was equivocal, the right was flexor.

Investigations

24.4.59. Bilateral carotid angiogram - slight shift of the mid line vessels to the left.

28.4.59. Ventriculogram - slight shift of ventricles to the left indicating the presence of a right sided expanding lesion probably mainly parietal.

11.5.59. Ventriculogram - ventricles now in mid line indicating resolution of the right sided expanding lesion.

Cerebrospinal /

Cerebrospinal fluid (from ventricles):-

	Cells	Chloride (as NaCl)	Protein	Sugar
11.5.59.	2/cu.mm.	690 mg%	72 mg%	73 mg%

Lange 2222100000

Virology:-

27.4.59. Serum complement fixation test - Titre < 8 for Herpes simplex lymphocytic choriomeningitis mumps "S" and "V"

12.5.59. Cerebrospinal fluid - chorioallantoic egg inoculation - no virus isolated.

26.5.59. Throat swabs (22.4.59) - No virus isolated by inoculation of mice (intracerebral), eggs (chorioallantoic) or HeLa tissue culture.

Cerebrospinal fluid (27.4.59) - No virus isolated in HeLa or amnion tissue cultures.

29.5.59. Complement fixation test - (date of serum 6.5.59 - convalescent). Titre < 8 for Herpes, lymphocytic choriomeningitis and Mumps "S" and "V".

Progress

The general condition of the patient began to improve slightly shortly after his transfer and he improved markedly after the first ventriculogram on 28.4.59. By 5.5.59 he was actively moving about in his cot and speaking a little although he gave small indication that he knew what had been said. Residual weakness of the limbs of the left side was evident. Ten days later (15.5.59) his progress was maintained and he was returned for final convalescence to his home hospital at Greenock. On this date he had only mild residual /

residual weakness more evident in the left hand than in the left leg.

The patient continued to improve gradually despite an intercurrent episode of enteritis but the left sided paresis of both arm and leg did not resolve completely. He was discharged from hospital on 16.6.59 and was to continue treatment for his muscular disability as an out-patient.

CASE 10

Sex: Male

Age: 15 years

Complaint

6.6.59. The patient complained of severe pain at the back of the head and of feverishness; these symptoms persisted for three days. The headache became worse on 9.6.59 and the patient vomited repeatedly.

Previous history

The patient did not give any medical history of note in infancy and early childhood apart from attacks of measles and whooping cough from which he had made normal recoveries. He had been vaccinated and immunised for diphtheria and whooping cough in infancy and had also received B.C.G. No history of recent infectious illness in his family or in other contacts was obtained. The present illness was abrupt in onset and was not preceded by any respiratory disorder.

State on admission

Temperature 103°F; pulse 103/min; respiration 24/min. The patient was a moderately ill boy of indifferent nutrition and development and of less than average intelligence. He was flushed and anxious but co-operative and fully orientated in time and space. No evidence of infection was noted in the respiratory system.

The pupils were unequal, the left was smaller than the /

the right but both reacted briskly to light. Very marked nuchal rigidity was present but all the cranial nerves were intact. There was no evidence of muscle weakness and all reflexes were present and equal; both plantar reflexes were flexor.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
10.6.59.	2/cu.mm.	730 mg%	20 mg%	78 mg%
11.6.59.	3/cu.mm.	750 mg%	15 mg%	103 mg%
22.6.59.	1/cu.mm.	730 mg%	20 mg%	72 mg%

Blood:-

Hb.	P.C.V.	M.C.H.C.	W.B.C.	E.S.R.
13.8 gm%	43	32%	10,600/cu.mm.	16 mm 1 hour.

Bacteriology:-

10.6.59. Throat swab : Heavy mixed growth of neisseria, streptococci, etc.

10.6.59. Post nasal swab : Moderate growth of Staphylococcus aureus.

11.6.59. Rectal swab: : No pathogens isolated.

Virology:-

Date of Serum:-	22.6.59	1.7.59
Complement Fixation Test		
Herpes	<8	<8
Lymphocytic choriomeningitis	<8	<8
Mumps "S"	<8	<8
" "V"	<8	<8
Adenovirus group	<8	<8

Stool:- Coxsackie A virus isolated in suckling mice 11.6.59.

Progress /

Progress

Twenty four hours after admission the patient was drowsy, confused and irritable; he resented examination. The physical signs remained unchanged. His condition improved gradually and forty eight hours later (13.6.59) he was afebrile and free of symptoms. Nuchal rigidity which had been steadily resolving was absent on this date. His subsequent progress was steady and nuchal rigidity was not again evident although the patient complained occasionally of moderate frontal headache.

The patient was discharged home on 26.7.59 and has remained well since this date.

CASE HISTORIES

GLASGOW GROUP

CASES 11 - 18

CASE HISTORIES

GLASGOW GROUP C CASES 11 and 12

CASE 11.

Sex: Male.

Age: 15 years 6 months.

Complaint

27.9.57. The patient was referred by his parents for medical advice because of disturbances of behaviour which had begun three days previously. He was irritable, abusive and aggressive.

Previous history

The patient was the second of a family of eight children all of whom were alive and well. The parents were both well and the father was employed as a labourer. The patient's birth and early childhood were normal. He had suffered from the usual childish ailments from which he had made normal recoveries. He first attended school at the age of five years and left on attaining fifteen years. He was a clever child, very popular alike with staff and pupils. He passed his qualifying examination at twelve years of age and went on to a secondary school. His record both in work and games was good. After leaving school he was employed on the railway as store-boy and was reported to be making good progress in his first employment.

A family history of mental illness was not elicited from either side.

Towards the end of September 1957 the whole family was affected /

affected by a febrile respiratory illness diagnosed as influenza at that time epidemic in the city. On 25.9.57 the patient woke up, complaining of headache. He was given some aspirin tablets; he thereafter fell into a deep sleep which lasted all day. The respiratory illness was not greatly improved and the patient had severe nasal catarrh and cough. On the following day (26.9.57) his mother noticed an alteration in the patient's face described as "a strange look "in the eyes". The patient read the morning newspaper and took breakfast; he remained in bed all day, singing continuously, although, when asked to stop, he denied that he had been singing. In the evening he began to behave in a disordered fashion. He rose from bed and wandered about the house without his pyjama trousers and began to swear at his mother, aunt and brother and to threaten them. At times he seemed "very far away" and was very irritable when disturbed. On the following day (27.9.57) he persisted in singing and said that beetles were running up and down the wall and that he had swallowed one. He was then referred to hospital.

State on admission

27.9.57. The patient was a well developed youth with a "strange facial expression". At the time of admission to hospital he was drowsy and could not be roused but some hours later he began to answer simple questions very slowly and in a whisper. Still later be became very irritable and resentful of examination. He was moved to anger at the slightest remark and his speech and reactions were quite uninhibited. He threatened /

threatened to stab his attendants and an attempt to effect lumbar puncture even after paraldehyde sedation was unsuccessful in the first instance.

Otherwise, physical examination of all systems, including the central nervous system gave essentially normal findings. Slight tenderness was, however, elicited in the epigastrium.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar	Globulin
1.10.57.	3/cu.mm.	720 mg%	25 mg%	Normal.	Normal.

Clear fluid not under obviously increased pressure.

Colloidal Gold Curve: 0000000000.

Wassermann Reaction : Negative.

Blood:-

28.9.57 W.B.Cs. 8,500/cu.mm.

Film. Normal white cell picture.

Wassermann and Kahn Tests: Negative.

X-ray examination:-

28.9.57. Chest: No abnormality detected.

4.10.57. Skull: No abnormality detected.

Electroencephalogram:-

10.10.57. Normal record.

Progress

The patient improved steadily while in hospital and was discharged well on 8.10.57.

CASE 12.

Sex: Male.

Age: 15 years.

Complaint

The patient showed disordered behaviour over a period of nine days after an attack of influenza in October 1957. Two further episodes of disordered behaviour of similar duration subsequently followed a sore throat and an attack of toothache.

Previous history

The patient was a schoolboy of rather less than average intelligence (intelligence quotient: 84). He was the first born of a pair of binovular male twins and the second of a family of six boys. The parents were of artisan class and the family circumstances were of acceptable standard. The twins were born after a normal pregnancy and confinement. The patient's history in infancy and early childhood was unremarkable. The patient throve and developed normally although he was known to be not as clever as his twin brother. The patient had chickenpox in childhood but did not have any other illnesses until October 1957, when the whole family became ill with a febrile respiratory disorder diagnosed as Asian influenza. All the other members of the family recovered normally but the patient did not do so. During his illness he began to rave and sing in a nonsensical manner, later, he relapsed into silence and developed a mask-like staring facies.

His /

His mother, suspecting delirium and pneumonia, sought medical advice but the patient was afebrile. At this time the patient was inaccessible and he was seen by a psychiatrist. He improved gradually in the succeeding days although he remained very somnolent. The possibility of his admission to hospital was considered at this time but was discarded as the patient appeared to have recovered nine days after the onset of the behaviour disorder.

About the end of October 1957 the patient complained of a sore throat and for a week after this ailment he was very somnolent and did not leave the house. He was moved by his mother from his usual sleeping quarters which he shared with two brothers into another, warmer, room. On the eighth day he showed some improvement and on the ninth day he got up and said "How did I get in here?". His mother, who had not been satisfied by previous medical advice now referred him to a child guidance clinic.

About mid November 1957, the patient suffered an attack of toothache and again became somnolent for a period of about nine days. On this occasion the attack was not as severe as previously but the patient was observed to be very pale. Recovery appeared to be complete after a period of nine days.

During these attacks the patient required two or three minutes before answering questions when he replied at all. He did not complain of excessive salivation or of double vision and squint was not observed by his attendants. The staring /

staring mask-like facies seen in the first attack did not recur. The patient was able to remember a headache during his attack of influenza but had no memory of the three periods of disordered behaviour. Questioned about the third attack he remembered having toothache and then remembered waking up eleven days later.

The patient has not had any other attacks since November 1957. He has some difficulty in getting up in the morning to go to school but this is explained by his habit of going late to bed. His mother, however, reported that he is sleepy at other times in the day and often falls asleep in a chair. In this respect he is unlike his brothers.

CASE HISTORIES

GLASGOW GROUP D CASES 13 - 18

CASE 13

Sex: Male

Age: 1 year 2 months

Complaint

12.7.58. The patient was admitted to hospital because of vomiting, irritability and convulsions of one day's duration.

Previous history

The patient was born after a normal pregnancy and confinement and had had no previous significant medical history before the onset of the present illness. The patient had been fully immunised both for diphtheria and poliomyelitis. He remained perfectly well until 11.7.58 when he became feverish and irritable and began to have frequent convulsions. The patient was sedated with ½ gr. nembutal prior to admission to hospital. When first seen by his medical attendant on 11.7.58 his temperature was 101.4°F; pulse 136/min; respiration 32/min., but no muscle weakness was found at this time.

State on admission

12.7.58. The patient was a well nourished healthy child partially sedated. In the upper respiratory passages the positive findings were of two small ulcers present on the palate; the tonsils were slightly inflamed. A small patch of exudate was present on the right tonsil. The upper cervical /

cervical lymph nodes were palpable on both sides of the neck. No abnormality was found in the circulatory or respiratory systems but examination of the nervous system revealed fairly well marked neck rigidity with an extensor plantar reflex on the left side. Kernig's sign was equivocal. A provisional diagnosis of meningismus secondary to tonsillitis or lymphocytic meningitis was made.

Investigations

Cerebrospinal fluid:-

	Cells	Protein	Sugar
12.7.58.	160/cu.mm.	25 mg%	145 mg%
14.7.58.	188/cu.mm.	25 mg%	144 mg%
15.7.58.	288/cu.mm.	35 mg%	63 mg%
18.7.58.	350/cu.mm.	89 mg%	63 mg%
26.7.58.	56/cu.mm.	69 mg%	59 mg%
31.7.58.	39/cu.mm.	83 mg%	53 mg%

Blood:-

	W.B.Cs.	Polymorphs	Lymphocytes	Monocytes
15.7.58.	8,800/cu.mm.	75%	22%	3%
16.7.58.	10,200/cu.mm.	77%	21%	2%
17.7.58.	6,800/cu.mm.	56%	40%	4%
18.7.58.	8,200/cu.mm.	70%	28%	2%
19.7.58.	6,800/cu.mm.			

	E.S.R.	Sugar
15.7.58.	14/32	74 mg%
17.7.58.	20 mm 1st hr.	

Bacteriology:- /

Bacteriology:-

Throat swab: No haemolytic streptococci were isolated. The normal flora of the throat were present on culture.

Cerebrospinal fluid : No organisms seen. Specimen sterile on routine culture.

Mantoux: 1/1000 negative.

Progress

Three days after admission the patient remained febrile with a furred tongue and inflamed throat. All limbs moved, but clinically the impression was again that the left arm and left leg moved less well than the right arm and right leg. No obvious cranial nerve lesions were present and examination of the optic fundi revealed only normal findings. Two days later the child showed general improvement and the pyrexia subsided. On 17.7.58 freer movements of the limbs and head were noted although movements of the left leg were still somewhat restricted. On 18.7.58 his general condition remained unchanged with persisting evidence of meningeal irritation and with stiffness of both legs. Two days later, on 20.7.58, the patient was afebrile and his general condition showed a definite improvement. By 25.7.58 the patient was sitting up, was much brighter generally and had remained afebrile. On this day he was standing and attempting to walk. 28.7.58, the patient was moving about freely and was allowed up for a short time. By the 6.8.58 the child clinically appeared well and was walking normally and did not display any residual nervous signs. He was discharged from hospital /

hospital for convalescence on this day.

The child was re-admitted to hospital on 11.8.58 with a complaint of earache of four days' duration.

State on admission

Temperature 100.2°F; pulse 136/min; respiration 32/min. The child appeared to be in pain in the left ear and left side of the neck. Examination of the upper respiratory passages showed a healthy mouth and throat and moist clean tongue. The tonsils were enlarged and slightly inflamed. The sub-mandibular glands were slightly enlarged. Examination of the nervous system was not possible in detail because of persistent writhing movements, but the patient appeared to move all limbs well. No abnormality was found in the abdomen or in the circulatory or respiratory systems.

Investigations

Cerebrospinal fluid:-

	Cells	Protein	Sugar
11.8.58.	20/cu.mm. (Lymphs)	73 mg%	63 mg%
12.8.58.	-	73 mg%	65 mg%
13.8.58.	27/cu.mm.	70 mg%	98 mg%

Blood:-

	W.B.Cs.	Polymorphs	Lymphocytes	E.S.R.
13.8.58.	12,000/cu.mm.	70%	30%	20 mm. 1st hour.

Virology:-

17.7.58. Stool swab - Negative for cytopathogenic agents including poliomyelitis, coxsackie and E.C.H.O.

Complement fixation test:- /

Complement Fixation Test:-

	Herpes simplex antigen
17.7.58.	128
7.8.58.	1024

Progress

14.8.58. The chief feature of the illness was now hyperkinesia. Some doubt was expressed as to whether hearing or sight were intact, but this was found difficult to assess in view of the depressed state of consciousness. The optic fundi appeared to be normal.

15.8.58. The child appeared drowsy and the general condition was poor with rising temperature. On this day he was transferred to a pediatric unit.

State on admission

Temperature 108.2°F; pulse 200/min; respiration rapid and grunting. The patient was a well nourished boy of good colour. He was very restless and from time to time he displayed opisthotonos. The tendon reflexes could not be elicited in the left arm but otherwise they were normal except in the lower limbs where the left plantar reflex was extensor and the right was equivocal. No abnormality was seen in the optic fundi.

The patient was treated by cold sponging and the pyrexia settled gradually. Initially, he was also given oxygen therapy and intravenous infusions of glucose saline.

Investigations /

Investigations

Cerebrospinal fluid:-

R.B.Cs.	W.B.Cs.	Protein
56/cu.mm.	11/cu.mm.	30 mg%

Skull X-ray:- Negative.

Heaf Tuberculin Test:- Negative.

Electroencephalogram:- Generalised high voltage, very slow activity on both sides.

Progress

The patient was treated by the exhibition of 100 milligrams daily of cortisone and this was given in gradually diminishing doses over a period of four weeks. Penicillin cover was given throughout. The patient remained very active and noisy but gradually be began to improve although some weakness of the left side persisted. Latterly he was able to pull himself to his feet and to walk quite well with only minimal support. He appeared to use his hands well. Much of his activity was, however, rather purposeless. He seemed to be best controlled by exhibition of phenobarbitone and primidone, and it was suggested that this treatment should be continued at home, to which he was discharged on 14.10.58.

CASE 14

Sex: Female

Age: 11 months

Complaint

On 18.7.58 the patient was observed to be listless and to have a sore throat. At the same time the patient had a productive cough.

Previous history

The patient, the third child of the family, was born after a normal pregnancy and confinement. Both parents were alive and well at the time of the patient's admission to hospital and no family history of serious illness was obtained. The patient had not been vaccinated or immunised.

State on admission

23.7.58. Temperature 99°F; pulse 120/min; respiration 28/min. The patient was a well nourished female child. The only positive physical findings in the respiratory system were those of moderately severe inflammation of the tonsils. Scattered rhonchi were present in both lungs. Examination of the remaining systems except the nervous system yielded essentially normal findings. On examination of the nervous system nuchal rigidity was evident although no muscular weakness was apparent and Kernig's sign was negative.

Investigations /

Investigations

Cerebrospinal fluid:-

	Cells	Protein	Sugar
23.7.58.	17/cu.mm.	15 mg%	51 mg%
25.7.58.	6/cu.mm.	20 mg%	71 mg%

Blood:-

	Hb.	W.B.Cs.
24.7.58.	11 gms%.	7,400/cu.mm.

Polymorphs	Lymphocytes	Basophils
42%	57%	1%

Bacteriology:-

23.7.58. Throat swab: A heavy growth of neisseria and pneumococcus with a few colonies of haemolytic streptococcus obtained.

25.7.58. Cerebrospinal fluid: Deposit heavily bloodstained. Scanty lymphocytes present. No organisms seen. No growth obtained.

28.7.58. Rectal swab: No pathogenic members of intestinal group isolated.

Virology:-

Serum - Complement fixation test:-

	Herpes antigen
24.7.58.	< 4
4.8.58.	128

25.7.58. Stool: Tissue culture for enteric virus - Negative.

4.8.58. Stool: Tissue culture for enteric virus - Negative.

Progress

24.7.58. A tentative diagnosis of non-paralytic poliomyelitis was made and the patient was treated with penicillin /

penicillin and sulphamezathine. Kernig's sign remained negative and muscle weakness was not apparent. The reflexes were normal but nuchal rigidity was still evident. The child responded well to treatment and four days later her general condition was satisfactory. The nuchal rigidity previously noted had disappeared. Subsequent progress was uneventful and she was discharged on 4.8.58.

CASE 15

Sex: Female

Age: 6 months.

Complaint

20.10.58. The child became ill on this day with vomiting which became worse at night. Her general condition deteriorated and two days later she was listless and refused food.

Previous history

The patient was born after a normal pregnancy and confinement. Both parents and an elder brother, aged four years, were alive and well. The child had not been immunised for diphtheria or smallpox and had not been given B.C.G. There was no previous history of illness.

State on admission

24.10.58. Temperature 102.4°F; pulse 60/min; respiration 40/min. The patient, an obese infant, was very pale and listless. Moderate inflammatory changes were present in the upper respiratory tract and examination of the respiratory system gave the signs of early broncho-pneumonia developing in both lung fields. Inflammatory changes were not present in the ears.

Examination of the nervous system gave signs of meningismus, and bulging of the anterior fontanelle was noted.

Shortly after admission convulsions occurred. The general /

general condition of the patient was poor and she was treated by sedation and the exhibition of chloramphenicol. Feeding was effected by intubation.

Investigations

Cerebrospinal fluid:-

	Cells	Protein	Sugar
24.10.58.	30/cu.mm.	40 mg%	61 mg%

Blood:-

	Hb.	W.B.Cs.	E.S.R.
25.10.58.	12.6 gms%	6,800/cu.mm.	21 mm 1 hour.

Bacteriology:-

25.10.58. Blood culture:

Digest broth: A heavy growth of Group A haemolytic streptococcus obtained. This strain is sensitive to all antibiotics.

Saponin broth: A growth of Coagulase negative staphylococcus obtained.

These divergent results suggest the possibility of contamination.

1.11.58. Faeces:- No pathogenc members of intestinal group isolated.

Virology:-

Serum - Complement Fixation Test:-

	Herpes antigen
25.10.58.	< 16
3.11.58.	512

11.11.58. Specimens of cerebral hemispheres, pons and medulla: No virus isolated by inoculation into adult mice (intracerebral), suckling mice (intra-:peritoneal), eggs (chorioallantoic) and tissue cultures (HeLa).

Progress /

Progress

Four days after admission the general condition of the patient remained unchanged, but although the convulsions were now controlled it was evident that both arms and legs were spastic. A slight but gradual improvement appeared during the following week, but the patient collapsed and died on 11.11.58.

Necropsy ($1\frac{1}{2}$ hours after death)

The body was that of a well nourished female child with no gross external evidence of disease. Examination of the respiratory system showed that the trachea and bronchi were free from obstruction and no inflammatory change was present. The pleural cavities were normal and the lungs showed no evidence of collapse or pneumonia. Examination of all the other systems, with the exception of the nervous system, yielded only normal findings.

The scalp and skull were normal. The meninges did not show any gross inflammatory changes. Some flattening of the cerebral convolutions and the surfaces of both cerebral hemispheres was evident and the brain was pale in colour. Section of the brain showed severe softening of all the cerebral cortex. The underlying white matter appeared normal and the basal nuclei showed no change apart from one very small haemorrhage (Fig. 1). The brain stem and cerebellum macroscopically were normal. The positive findings were confined to extensive and severe softening of all the cerebral cortex.

Morbid /

Morbid histology

The most severe lesions were found in the cortical ribbon of both cerebral hemispheres which showed the features of widespread disorganisation and necrosis in all sections examined and this suggested a process of disintegration occurring simultaneously over all the surfaces of the cerebral hemispheres. The cortex appeared as a ribbon of oedematous tissue superimposed upon the underlying white matter and infiltrated by very numerous gitter cells and by inflammatory cells. The normal architecture was greatly disturbed and in many fields it was difficult to identify with certainty any nerve cells. In some fields the outlines of penetrating vessels were still discernible and here the inflammatory cells which included numerous round cells together with some polymorphs and plasma cells were more numerous. In the white matter of the cerebral hemispheres the lesions were perivascular in site and the small veins were most often affected. Widespread and severe venous congestion was generalised and all degrees of vascular damage from endothelial swelling to frank vascular necrosis were frequently seen. These vascular changes were associated with local perivascular haemorrhage and the whole focus was infiltrated by small round cells. The overlying leptomeninges in these sections from the cerebral hemispheres were infiltrated by proteinous exudate and small round cells together with plasma cells which were more numerous here than elsewhere. The vessels of the leptomeninges which were very congested /

congested also showed all variations of endothelial damage from swelling to necrosis and these changes were associated with extravasations of erythrocytes.

In the pons, the lesions again were perivascular and were most numerous in the white matter where also occasional nodules of microglial proliferation were seen (Fig. 8). The veins and venules again were most affected but the capillaries were spared. The same features already noted in the white matter of the cerebral hemispheres were evident also at this level but in general they were less severe. Small round cells were predominant in cuffing of affected vessels. The vessels of the leptomeninges of the pons showed generalised congestion with moderate proteinous exudate, extravasations of erythrocytes and round cell and polymorph infiltration in the subarachnoid space. These changes were more marked on the ventral aspect of the pons. The fourth ventricle and its ependyma together with portions of choroid plexus at this level showed normal appearances.

Within the cerebellum moderate venous congestion was evident in the cortex. Perivenous and perivenular lesions of the same kind as those seen in the cerebral hemispheres and in the pons were also present here but were much less severe. The appearances of the cerebellar cortex were normal. The changes in the leptomeninges of the cerebellum were similar to those seen elsewhere in these structures but much less severe.

Inclusion bodies were not found in any of the fields examined.

CASE 15

FIGURES 1 - 12

CASE 15

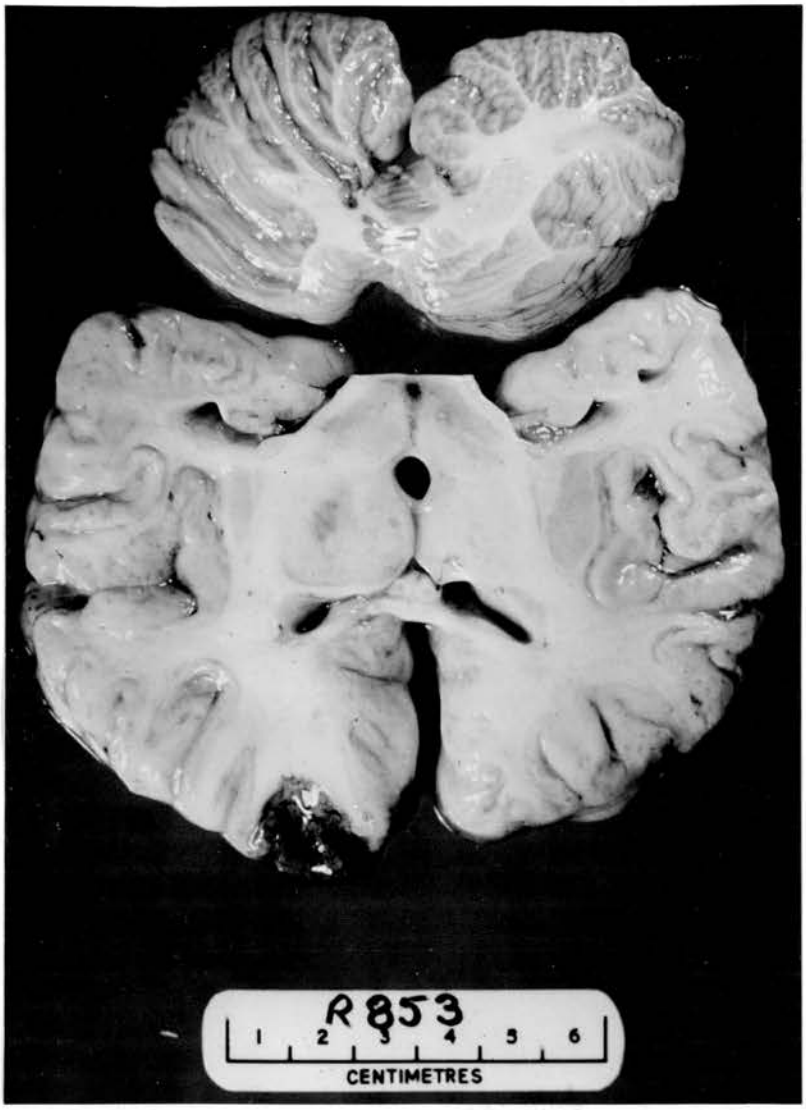

Fig. (1). Cerebral and cerebellar hemispheres:

Generalised softening of the cortical ribbon of the cerebrum is evident with a haemorrhagic lesion near the sagittal sulcus in the right hemisphere. A single small haemorrhagic lesion is present in the right basal ganglia. The appearances of the cerebellum are within normal limits.

CASE 15

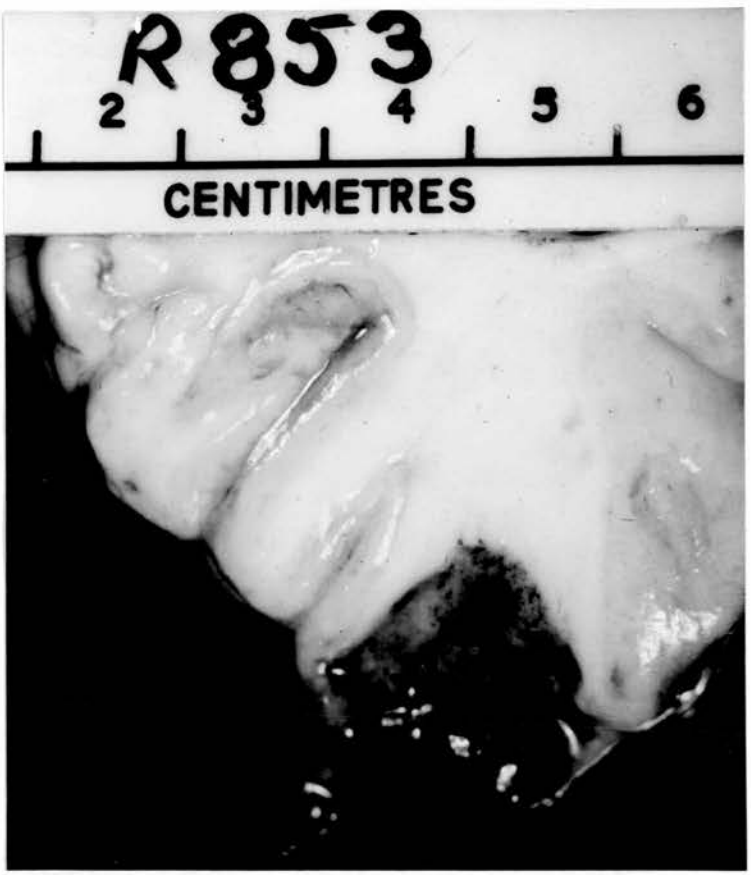

Fig. (2). Right cerebral hemisphere.

Detail of haemorrhagic softening in the cortex and subjacent tissues.

CASE 15

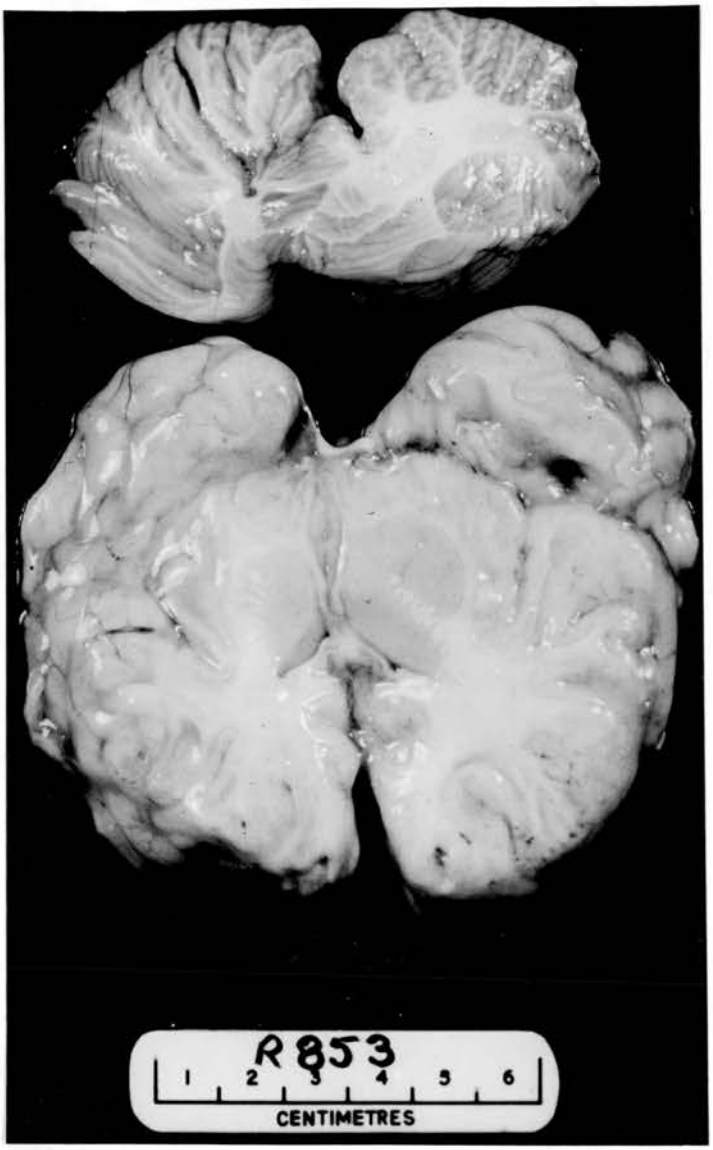

Fig. (3). Frontal lobes of cerebrum.

Extensive softening of the cortical ribbon is present in both cerebral hemispheres. Small haemorrhagic areas are evident about the vertex of the right hemisphere.

CASE 15

Fig. (4). Right cerebral hemisphere frontal lobe.

Detail of haemorrhagic areas in cortical necrosis.

CASE 15

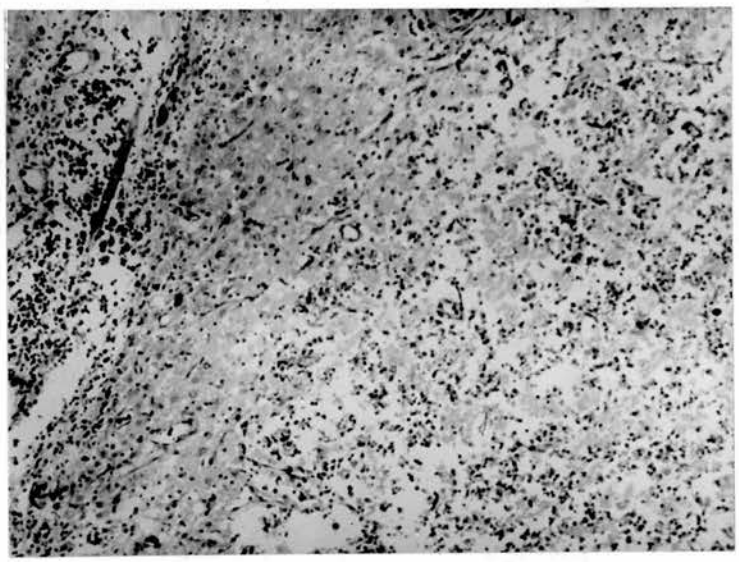

Fig. (5). Motor cortex left cerebral hemisphere.

There is disorganisation of cortical and medullary structures with extensive infiltration by inflammatory and gitter cells.
(Haemalum and eosin X 110).

CASE 15

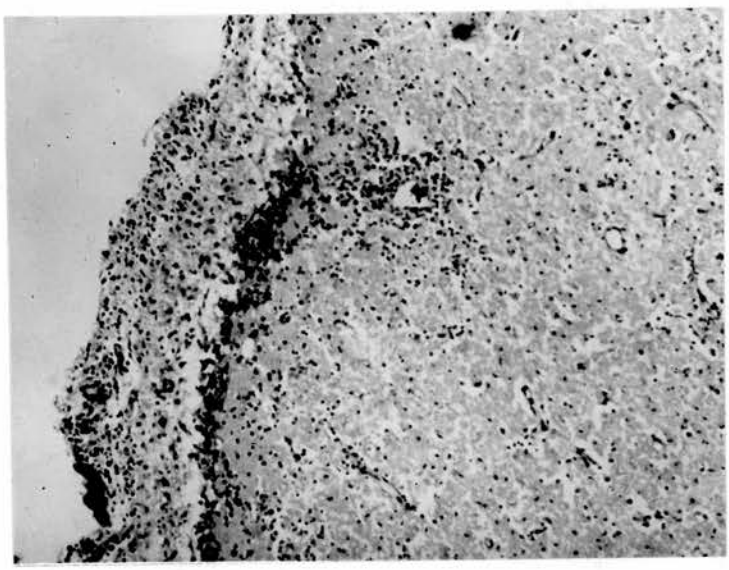

Fig. (6). Cortex; left frontal lobe.

The cortex is largely destroyed; a dense cellular band extends between the deeper layers of cortex and the underlying white matter. (Haemalum and eosin X 125).

CASE 15

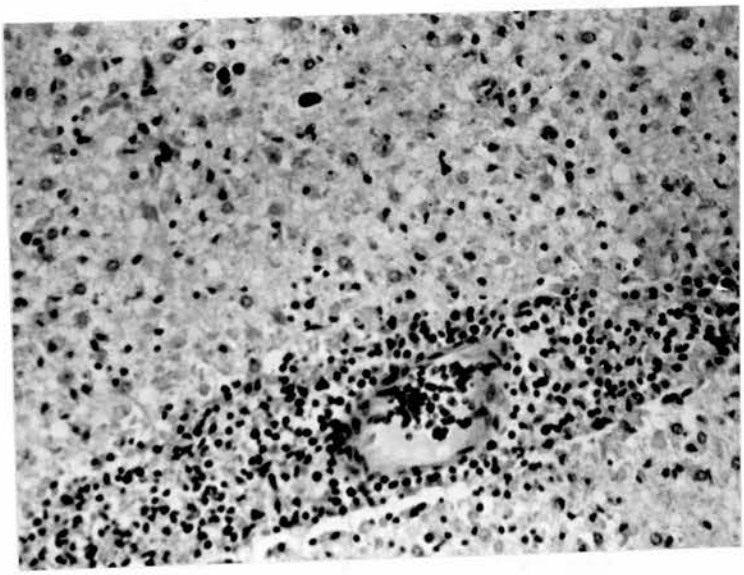

Fig. (7). White matter right parietal lobe.

Dense cuffing of a small vein with small round cells.
(Haemalum and eosin X 165).

CASE 15

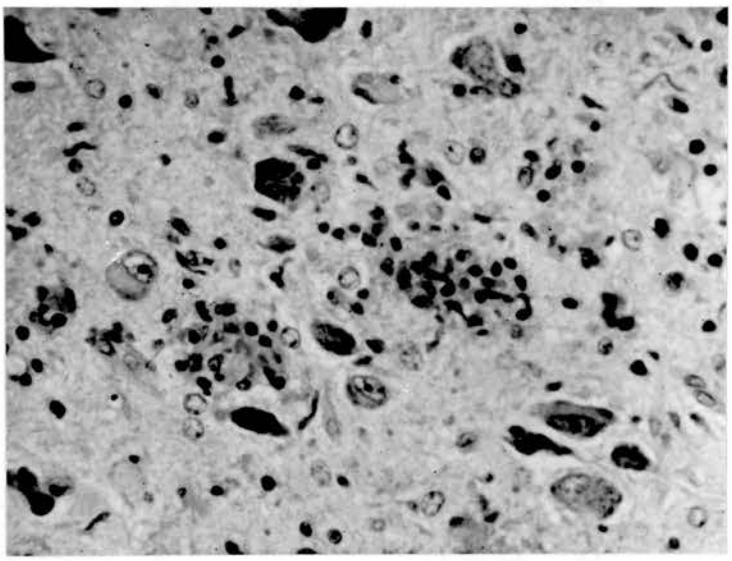

Fig. (8). Pons.

Two small foci of microglial proliferation are evident and nerve cells show margination of chromatin.
(Haemalum and eosin X 310).

CASE 15

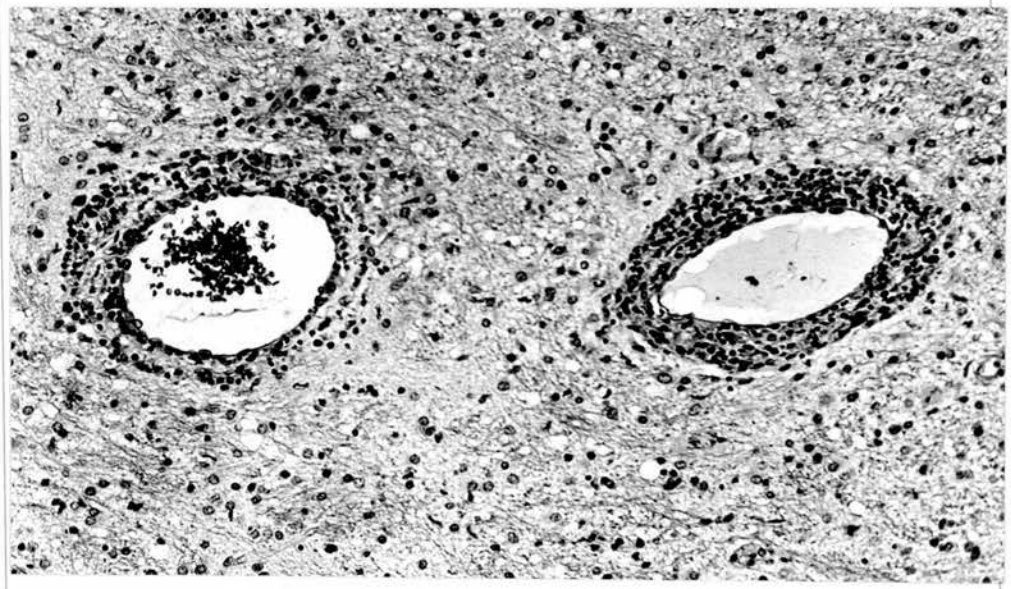

Fig. (9). White matter left parietal lobe.

Two small veins show well marked cuffing in the Virchow Robin spaces.
(Haemalum and eosin; X 150).

CASE 15

Fig. (10). Right frontal lobe, meninges, cortex and sub-cortical medulla.

Dense inflammatory infiltration is evident in the leptomeninges. The cortex and subjacent medullary fibres show severe disorganisation with inflammatory and gitter cell infiltration. (Haemalum and eosin; X 180).

CASE 15

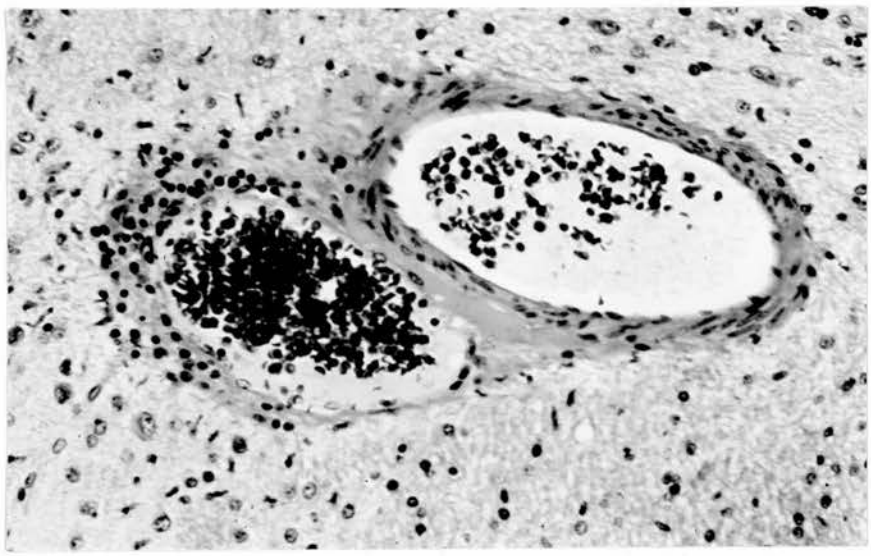

Fig. (11). Pons.

A small vein is undergoing disorganisation with cellular infiltration in the wall of the vessel. (Haemalum and eosin; X 200).

CASE 15

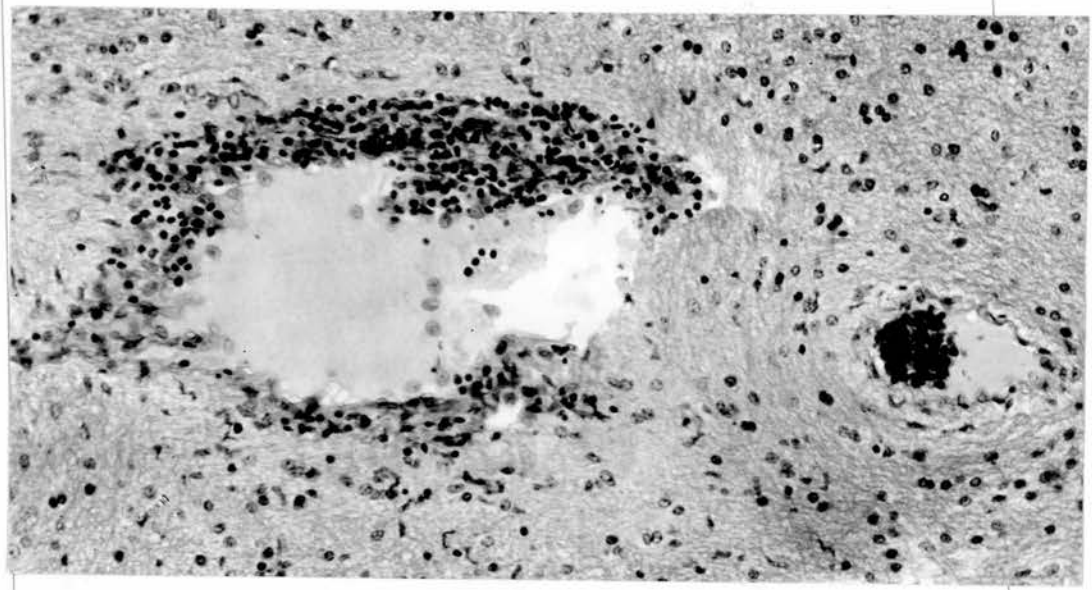

Fig. (12). Right cerebellar hemisphere; white matter.

A small vein almost completely disorganised shows dense cellular infiltration.
(Haemalum and eosin; X 200).

CASE 16

Sex: Male

Age: 9 months

Complaint

For a period of two days before admission the patient had been listless and anorexic with intermittent vomiting.

Previous history

The patient was born after a normal pregnancy and confinement, and had been in normal health until the present illness. At birth he had been given B.C.G. and at the age of three months had been immunised against whooping cough, smallpox and diphtheria.

State on admission

2.11.58. Temperature 99°F; pulse 156/min; respiration 44/min. The patient, a child of good nutrition, was acutely ill and comatose. The appearances at this time suggested a state of continuous convulsion and the condition of the patient alternated from one of extreme limpness and flaccidity to one of complete spasticity. The patient was treated by penicillin, oxygen and eucortone. The positive clinical findings were those of moderate inflammation of the fauces and of a furred tongue. Examination of the respiratory system disclosed scattered rhonchi in both lung fields and these were more numerous posteriorly on the left side. No other abnormalities were found.

Investigations /

Investigations

Cerebrospinal fluid:-

	Cells	Protein	Sugar
3.11.58.	12/cu.mm.	40 mg%	127 mg%
6.11.58.	53/cu.mm.	20 mg%	60 mg%

Urine:-

3.11.58. Urea - 2.5 gms%

Paper chromatography of urine showed an increase in the number and amount of amino acids excreted.

Vomit:-

3.11.58. Occult blood - Positive.

Blood:-

	Hb.	W.B.Cs.	E.S.R.
3.11.58.	10.5 gms%	10,400/cu.mm.	10 mm 1 hour.

	Polymorphs	Lymphocytes	Sugar	Urea
3.11.58.	60%	29%	113 mg%	48 mg%

Bacteriology:-

3.11.58. Throat swab: A few colonies of Staphylococcus present. This strain does not produce coagulase.

4.11.58. Blood: No growth obtained after 48 hours incubation.

Virology:-

3.11.58. Stool : Tissue culture - Negative.

Cerebrospinal fluid: Tissue culture - Negative.

Serum : Complement Fixation Test -

	Herpes antigen
3.11.58.	<16
25.11.58.	128

Progress /

Progress

Two days after admission a transient punctate erythematous rash was observed on the trunk and the patient was fretful and drowsy, but vomiting had ceased. Forty eight hours later, 6.11.58, the patient was still drowsy, but was eating and drinking well. He continued to improve steadily, and by 10.11.58 was showing no abnormality. He was discharged on 17.11.58.

CASE 17

Sex: Female

Age: 46 years

Complaint

20.11.58. The patient was admitted to hospital in status epilepticus.

Previous history

The patient had been a healthy woman and the only medical history of note obtained was that she had become semi-stuporose during an attack of influenza in 1956. On this occasion the patient was admitted to hospital but had recovered full consciousness shortly after admission.

Nine days before the present admission (11.11.58) the patient had developed a febrile illness with severe headache but no cough. The patient began vomiting on 15.11.58 and vomited again on 17.11.58. On 19.11.58 the patient began to have "fits". These episodes began with a period of hyperventilation followed by tonic contractions of the hands and forearms. The head was deviated to the left and twitching occurred in the face and limbs on both sides. These disturbances occurred at intervals of one to two hours, both by day and night. The patient lost consciousness for a short period after each episode and was drowsy in the intervals between them.

The only drugs taken were the powders prescribed for the febrile illness.

State /

State on admission

20.11.58. Temperature 100°F; pulse 85/min; respiration 24/min. The patient was comatose and responded only to very painful stimuli. The corneal reflex was elicited. The limbs were hypertonic; the right plantar reflex was flexor, the left equivocal. The pupils were small but equal and reacted sluggishly to light. Papilloedema was not present. Moderate nuchal rigidity was observed.

A generalised macular rash of the trunk and proximal segments of the limbs was present. This was confluent in some areas and faded on pressure. Irregular erythematous patches with well defined edges were observed on the forehead, cheeks, palms and fingers. The tongue was dry and coated.

Examination of the other systems gave findings within normal limits.

Investigations

Cerebrospinal fluid:-

	Cells	Globulin (Pandy)	Chlorides	Total Protein	Sugar	Culture
20.11.58.	4/cu.mm. + a few R.B.Cs.	Not increased.	720 mg%	20 mg%	Normal (Benedict's)	-
27.11.58.	3/cu.mm.	Not increased.	720 mg%	10 mg%	Normal (Benedict's)	No growth.

20.11.58. Colloidal Gold Curve: 0000000000

Haematology:-

	Hb.	W.B.Cs.	L.E. cells
20.11.58.	-	-	No L.E. cells detected in defibrinated blood.
21.11.58.	13.1 gms%	12,000/cu.mm.	

Biochemistry /

Biochemistry:-

20.11.58.	Serum	Calcium	11.9 mg%
		Inorganic Phosphate	4.5 mgP%
		Urea	19.0 mg%
		Protein	6.5 g%
		Chloride	106 m.equiv/litre.
		Alkali Reserve	20 m.equiv/litre.
		Potassium	2.1 m.equiv/litre.
	Blood	Sugar	163 mg%.
21.11.58.	Serum	Protein	6.7 g%
		Albumin	3.7 g%
		Globulin	3.0 g%
		Bilirubin	1.1 mg%
		Alkaline Phosphatase	7 KA units%
		Thymol turbidity	1 unit.
		Thymol flocculation	Negative.
		Urea	38 mg%
		Chloride	103 m.equiv/litre.
		Alkali Reserve	31 m.equiv/litre.
		Potassium	3.0 m.equiv/litre.
25.11.58.	Blood	Sugar	150 mg%
27.11.58.	Serum	Potassium	3.5 m.equiv/litre.

Bacteriology:-

20.11.58. Blood: No growth after 48 hours incubation.

24.11.58. Blood: No growth after 48 hours incubation.

24.11.58. Catheter specimen of Urine: Direct - Pus cells +.

21.11.58. Stool: Culture - A heavy growth of Staphylococcus aureus (coagulase positive).

28.11.58. Stool: Direct - A few Gram positive diplococci seen.
Culture - A moderate growth of Staphylo-:coccus aureus (coagulase positive).

Virology:-

26.11.58. Stool: Tissue culture for enteric virus - Negative.

Complement /

Complement fixation tests on sera:-

	Herpes simplex	Mumps	Lymphocytic choriomeningitis
26.11.58.	< 8	< 8	< 8
10.12.58.	32	< 8	< 8
18.12.58.	32	< 8	< 8

E.E.G. examination:

2.12.58. The record shows frequent outbursts of high voltage synchronous delta activity generally. This is too severe to be a post-ictal phenomenon, and there is almost certainly an organic pathology.

18.12.58. This E.E.G. shows some improvement, but is still quite abnormal.

9.1.59. The record is still improving, but is still definitely abnormal. The slow return to normality suggests that there has been an organic lesion.

Wassermann reaction:-

21.11.58. Cerebrospinal fluid - Wassermann reaction: Negative.

26.11.58. Wassermann reaction: Negative.
Kahn test: Negative.

Progress

For three days after admission the patient remained comatose although the level of coma became gradually less deep. From time to time convulsive seizures occurred and these were associated with incontinence of urine and faeces.

The skin rash noted on admission faded gradually and had cleared after a week in hospital. The patient's immobility gave rise to concern about respiratory infection but this was combated by careful nursing and exhibition of antibiotics.

4.12.58. The level of consciousness continued to improve /

improve and by this date the patient was somnolent but able to respond slowly to questioning. Only slight dappled pigmentation remained at the site of the previous rash.

6.12.58. The patient displayed retrograde amnesia for the entire period of the illness.

2.1.59. The general condition of the patient was much improved and she was walking about. Her memory, however, remained poor and she was unable to recall the death of her husband.

The patient continued to improve slowly and by 17.1.59 was considered fit for discharge. In view of some degree of persistent retrograde amnesia and emotional lability the patient became the responsibility of a psychiatric clinic and was to be reviewed periodically.

CASE 18

Sex: Male

Age:58 years

Complaint

23.4.59. The patient complained of numbness and paresis of both lower limbs with left shoulder pain and paresis of left arm. These symptoms were present for a week before admission to hospital.

Previous history

The patient was well until 16.4.59, exactly a fortnight before his admission to hospital. On the day of onset of illness he had had a fit of shivering and had felt generally unwell; this had been diagnosed as "influenza". When questioned after admission he did not recall having had any headache or pains or stiffness in the neck or limbs. A week after onset both legs began to feel numb and prickly and at the same time muscular weakness developed. Five days later he felt pain in his left shoulder, radiating down his left arm, which also became weak. There was no interference with bowel function but occasionally there was slight difficulty in beginning micturition.

Before the onset of the present illness he had enjoyed good health.

State on admission

The patient was a well nourished man in late middle age, fully conscious, alert and co-operative. There was slight /

slight nuchal rigidity but Kernig's sign was negative in both legs. There were no herpetic lesions. There was slight motor weakness of the right lower face on testing. The only other abnormality on routine examination of the cranial nerves was inequality of the pupils, the right being greater than the left. Motor power of the left arm was noticeably less than that of the right on admission. The left arm was maintained in constant flexion at the elbow and passive attempts to straighten it demonstrated the severe spasticity of the flexor muscles.

Both legs showed severe motor loss; the right leg could be raised voluntarily from the bed but even this movement was impossible in the case of the left leg. Both legs were severely spastic.

All the deep reflexes of the limbs were hyperactive, those of the left arm more so than those of the right. Both plantar reflexes were extensor.

There was also sensory impairment on admission, namely loss of tactile, pain and temperature sensations over the right leg and lower right side of trunk, the left side of the body being entirely unaffected at this time.

Investigations

Cerebrospinal fluid:-

	Cells	Chloride	Protein	Sugar
30.4.59.	2/cu.mm. (Lymphocytes) A few red cells.	760 mg%	50 mg%	44 mg%

30.4.59. Wassermann - Negative.

30.4.59. Colloidal Gold - Negative.

Blood /

Blood:- Routine blood examinations at admission showed only a mild neutrophil polymorph leucocytosis at first (13,100) which soon disappeared.

1.5.59. Kahn - Negative.

3.5.59. Urea - 50 mg%.

Virology:-

Complement Fixation Test:

	Herpes
2.5.59.	64
12.5.59.	16
20.5.59.	< 8
15.6.59.	< 4

No virus was isolated from any specimens submitted.

Progress

During the first three days of his hospital residence some extension of paresis occurred in the left arm; there was practically no grip in the left hand and the movements at elbow and shoulder became flail-like. The muscles of respiration became involved to the extent of diminution of rib movements on the right side compared to those of the left and it became impossible to detect the respiratory movements of the abdominal wall.

The sensory loss spread rapidly; both lower limbs were now involved in the loss of tactile sensation, the upper level being at the lower abdomen. At the same time a new area of sensory loss developed, distinct from the foregoing. This was a zone involving both arms, the upper part of the chest in front and the scapular areas behind.

Over /

Over this area, tactile sensibility was lost and pinpricks greatly diminished. Soon, however, these zones became less well defined and appeared to merge into one another on the trunk but the right lower limb and the right side of trunk were always more anaesthetic to pinpricks than the corresponding areas on the left side.

By the ninth day after admission improvement had begun. The patient could make some voluntary extension and flexion of the left elbow and with much effort he could flex both knees to a slight extent. Spasticity was still a feature of the left arm and of both legs. After another three weeks (i.e. by the end of his first month in hospital) he could perform the grosser movements of the left arm although they were still flail-like and uncertain but left grip and finger movements were still very poor. For the first time, slight motor weakness was detectable in the right hand and arm but only when the examiner applied counter-resistance to test movements by the patient. There was still slight weakness of the right lower face. Sometimes, however, the face was passive and expressionless. The slight inequality of the pupils persisted. By this time, also, the range of voluntary movement of the legs was increasing although the action was stiff and laborious and any attempts by the examiner to increase the range revealed the severe spasticity of the legs and caused pain. Sensibility was also improving. Light touch was now felt over the legs although sometimes it was poorly localised but pinpricks were still unappreciated /

unappreciated over the right foot and leg and in patches over the right thigh. Pinpricks were felt normally over the arms and upper trunk by this time. A new sign was muscular atrophy of the left arm, the large muscle groups as well as the small muscles of the hands being involved. The right thigh also showed some wasting. Bladder and bowel functions had become mechanical reflexes by this time.

Throughout his second month in hospital there were only a few changes in the physical signs. Two out of the three deep reflexes of the left arm became abolished although severe spasticity continued. The right hand showed more definite evidence of being involved in so far as finger movements became clumsy and slight spasticity could be detected in the right arm. There was no return of power in the finer movements of the feet and toes but in spite of this severe dysfunction, he was daily lifted out of bed into an easy chair about this time.

During his third month in hospital there was further significant change in the deep reflexes, namely those of the right arm became very sluggish and all three in the left arm became lost. Motor power in the right arm was fairly well maintained however. The left grip was still extremely poor although voluntary movement of the left elbow and shoulder were showing further improvement. With regard to motor power in the legs, this was improving and the patient could now move his toes at will and flex and extend the large joints more strongly. The thoracic movements of respiration were /

were still very poor but diaphragmatic action appeared to be free. On the other hand examination of sensations showed extension of loss during this month, namely, the right side of the trunk and the right scapular region showed diminution of thermal sensibility. Similar default was found in patches over the right lower limb and left thigh, the latter for a few days only. Pain sensation was still blunted over the right thigh and, in the same region, tactile also.

By the end of the fourth month in hospital the patient was able to take a few halting steps, supported or steadied by one or two nurses.

During the fifth and last month of his stay, the chief physical signs were still those of severe involvement of the pyramidal tracts supplying the legs. The deep reflexes in both upper limbs still could not be elicited. The pupils were now equal; their reflexes were, as before, active. There was still slight weakness of the right lower face. The remaining musculature of the left arm and hand was being exercised to good purpose by the patient and the sensory impairment was becoming less conspicuous - the left foot, as well as the right, and also the left leg showed only slight impairment of touch, thermal and pain sensations. This was his clinical condition on dismissal from hospital after a stay of five months.